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Cancer, Ophthalmology & Pediatric

Special Emphasis on Prostate Cancer

Chlorine Dioxide Gas-Releasing Agents

Highlights

Risk Factors in Hypertensive Patients

Prevention and Treatment Opportunity

Discovering Thoughts, Inventing Future

VOLUME 23 ISSUE 2 VERSION 1.0

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Relationship between COVID-19 and use of Chlorine Dioxide Gas-Releasing Agents in Elementary Schools

By Yoshinori Kubo, Takanori Miura, Kaoru Obinata, Ken Hisata, Mitsuyoshi Suzuki, Eisuke Inage, Naotake Yanagisawa, Hiromichi Shoji, Norio Ogata, Jo Shibata, Takashi Shibata & Toshiaki Shimizu

Juntendo University

Abstract- Chlorine dioxide has an inactivating effect on various types of viruses in vitro, including severe acute respiratory syndrome coronavirus 2. Therefore, chlorine dioxide gas can be used as a new preventive measure against coronavirus disease 19 (COVID-19). However, no studies have been conducted to investigate the relationship between the incidence of COVID-19 and chlorine dioxide. We retrospectively studied the occurrence of COVID-19 in 164 public elementary schools under the jurisdiction of boards of education located in urban areas in Japan, provided with chlorine dioxide gas-releasing agents or not, from January to March 2022. The odds of developing COVID-19 were lower (odds ratio: 0.934, 95% confidence interval: 0.895–0.975) in schools provided with chlorine dioxide gas-releasing agents than in schools without them. This suggested a relationship between the use of chlorine dioxide-releasing agents and the incidence of COVID-19. Further studies are needed to prove a causal relationship between them.

Keywords: chlorine dioxide, COVID-19, infection prevention, elementary school, viral infectivity.

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Relationship between COVID-19 and use of Chlorine Dioxide Gas-Releasing Agents in Elementary Schools

Yoshinori Kubo [α], Takanori Miura [σ], Kaoru Obinata [ρ], Ken Hisata [ω], Mitsuyoshi Suzuki [¥], Eisuke Inage [§], Naotake Yanagisawa [χ], Hiromichi Shoji [ν], Norio Ogata [Θ], Jo Shibata [ζ], Takashi Shibata [£] & Toshiaki Shimizu [€]

Abstract- **Chlorine dioxide has an inactivating effect on various types of viruses in vitro, including severe acute respiratory syndrome coronavirus 2. Therefore, chlorine dioxide gas can be used as a new preventive measure against coronavirus disease 19 (COVID-19). However, no studies have been conducted to investigate the relationship between the incidence of COVID-19 and chlorine dioxide. We retrospectively studied the occurrence of COVID-19 in 164 public elementary schools under the jurisdiction of boards of education located in urban areas in Japan, provided with chlorine dioxide gas-releasing agents or not, from January to March 2022. The odds of developing COVID-19 were lower (odds ratio: 0.934, 95% confidence interval: 0.895–0.975) in schools provided with chlorine dioxide gas-releasing agents than in schools without them. This suggested a relationship between the use of chlorine dioxide-releasing agents and the incidence of COVID-19. Further studies are needed to prove a causal relationship between them.**

Keywords: chlorine dioxide, COVID-19, infection prevention, elementary school, viral infectivity.

I. Introduction

Since December 2019, coronavirus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Shang et al., 2020; Zhou et al., 2020) has been a global public health problem (Chen et al., 2020; Xu et al., 2020). Although pediatric patients with COVID-19 often have a milder course than adults, the COVID-19 infection has had a negative impact on children in terms of lost learning opportunities, malnutrition, poverty, and disruption of health services such as routine childhood immunizations (UNICEF, 2022). In the first and second waves of COVID-19 in Japan, the proportion of cases under 20 years of age was less than 15% (Imamura et al., 2021), and children did not suffer from secondary infections (Ko et al., 2022). However, in the sixth wave of the omicron variant, the proportion of cases under 20 years of age rose to 35% (Aizawa et al., 2022). Standard infection control measures include routine precautions such as hand washing, wearing masks, and environmental cleaning. Thorough implementation of these measures is important for the prevention of infection. However, it has been reported that young children often not wash properly their hands and hand washing is less effective. (Harada, 2004)

In addition, in terms of environmental cleaning, it is practically impossible to clean areas where hand contact occurs with high frequency, and standard precautions alone are not sufficient to prevent infection. Despite the prevalence of highly infectious variants in all age groups, parents are hesitant to vaccinate their children (Horiuchi et al., 2021; Yoda & Katsuyama, 2021). Therefore, to reduce the adverse effects of COVID-19 on children and prevent the spread of infection, it is desirable to reduce the incidence of COVID-19 through new preventive measures.

SARS-CoV-2 is transmitted among human beings primarily through close contact in confined spaces, droplets of respiratory origin, and contaminated surfaces (Cheng et al., 2020; Lai et al., 2020; Sungnak et al., 2020). SARS-CoV-2 can remain on the surface of the vector for several days (Chin et al., 2020; van Doremalen et al., 2020) and is stable for several hours if aerosolized (van Doremalen et al., 2020). Therefore, environmental factors can have a significant impact on transmission in buildings where people are in close proximity, such as schools (Azuma, Kagi, et al., 2020; Azuma, Yanagi, et al., 2020). Especially in Japan, during the sixth wave of SARS-CoV-2 infection, the proportion of infections in children in schools, nursery schools, and kindergartens increased, while the proportion of infection in the family, the main source of infection, decreased (Aizawa et al., 2022). Therefore, schools are considered an important place for the prevention of COVID-19 in children.

Chlorine dioxide (CD) exists as a diffusible gas at room temperature that can be distributed over a wide area (Gates, 1998). The effectiveness of low-concentration CD gas, which poses almost no risk to the human body, was demonstrated in an in vitro

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experiment in a closed space in which 0.01 ppmv CD gas inactivated more than 99% of all floating viruses (Ogata et al., 2016). More than 99% of the viruses adhering to the surface of objects were also inactivated by 0.007 ppmv CD gas (Morino et al., 2013).In vivo experiments suggested that 0.03 ppmv CD gas prevented influenza infection in mice (Ogata & Shibata, 2008). In vitro experiments using a CD gas-releasing agent have also shown inactivation of the avian influenza virus A (H7N9) (Sun et al., 2022). Further, studies in humans have suggested that the use of CD gas-releasing agents is effective against viral infections (Mimura et al., 2010; Ogata & Shibata, 2009).

Although CD gas-releasing agents can be expected to be useful for COVID-19 prophylaxis, no studies have been conducted to investigate the relationship between COVID-19 infection and CD gas-releasing agents. Therefore, the purpose of this study was to conduct a retrospective study of the relationship between the use of CD gas-releasing agents and the incidence of COVID-19 in elementary schools.

II. Material and Methods

a) Design

This multicenter, retrospective study investigated the relationship between the incidence of COVID-19 and the use of CD gas-releasing, from January to March 2022, using a database created by the City Board of Education. This study was approved by the Juntendo University School of Medicine Medical Research Ethics Committee (Research Project No. E22-0382).

b) Subjects

The subjects of this study were first- to sixth-grade (approximately 6 to 12 years old) male and female students in public elementary schools under the jurisdiction of a municipal board of education in an urban area in Japan. Since there was no precedent for this study, the sample size could not be calculated. No exclusion criteria were established as this was an exploratory study.

c) CD gas-releasing agent

CD gas-releasing agents (Cleverin® pro Gel Large type for 50m2(Taiko Pharmaceutical Co.) and Cleverin Pro Pouch type for 30 m2, Taiko Pharmaceutical Co., Ltd., Japan) are made by adding sodium dihydrogen phosphate to sodium chlorite and solidifying the mixture by adding superabsorbent polymers, which then generate and release CD gas continuously for several months. Those agents, which can be safely used in an inhabited environment, were provided free of charge by Taiko Pharmaceutical Co., Ltd. to city school boards for marketing purposes. They were further distributed by city school boards to elementary schools that requested them from January 2022 through March 2022. It was recommended that those agents be provided in classrooms at a rate of one unit per 30 m2 or 50 m2 in the case of Cleverin Pro Pouch type or Placeable type, respectively.

d) Incidence of COVID-19

The number of infections of COVID-19 was investigated in all elementary schools from January to March 2022. The parents of the children were requested to notify the schools when the PCR test for COVID-19 was positive, when the antigen test was positive, or when a physician determined that COVID-19 was strongly suspected. These reports were compiled by the elementary schools and reported to the city's board of education. The city school board created a database of the CD gas-releasing agents provided and the number of COVID-19 infections.

e) Statistical analysis

The distribution by a number of elementary school students was shown as the median (25th–75th percentile values), since the Kolmogorov-Smirnov normality test did not allow for a normal distribution. The association between the use of CD gas-releasing agents and the incidence of COVID-19 was analyzed using crude odds ratios of the subjects who suffered from COVID-19. Incidence as cases were defined as the number of reported COVID-19 incidences, and controls (non-incidence) were defined as the number of children minus the number of reported COVID-19 infections. The significance level was $p<0.05$, and IBM SPSS Statistics® ver. 28 was used for statistical analysis.

III. Results

A summary of the elementary schools analyzed in this study is shown in Table 1. Sixty-eight elementary schools (n = 34,810) did not use any CD gas-releasing agent, whereas 96 (n = 38,714) used those agents.

Table 2 shows the odds ratio for incident COVID-19. Elementary schools that did not use chlorine dioxide-releasing agents had higher odds (odds ratio: 0.934, 95% confidence interval: 0.895–0.975) of COVID-19 incidence than those that did.

IV. Discussion

This exploratory study investigated the relationship between the use of CD gas-releasing agents in classrooms and COVID-19 infections in elementary schools and showed that elementary schools that used those agents had significantly lower odds ratios for COVID-19 incidence than those that did not.

A previous study showed that in an intervention study of Ground Self-Defense Forces personnel, a group that used those CD gas-releasing agents in a room had significantly lower numbers of cases of influenza-like illnesses than the non-intervention group

(Mimura et al., 2010). In addition, a retrospective observational study of elementary school students reported significantly lower cumulative absenteeism rates in classes where those CD gas-releasing agents were used than in classes where they were not used (Ogata & Shibata, 2009). The results of this study support the findings of these previous studies. A potential mechanism by which the CD gas-releasing agent suppressed COVID-19 infections is that CD gas, once dissolved in water, reduces the binding activity of the SARS-CoV-2 spike protein as demonstrated in in vivo experiments (Ogata & Miura, 2020, 2021). It has been suggested that this mechanism can reduce the viral infectivity of SARS-CoV-2 (Hatanaka et al., 2021). In summary, these findings suggest that the use of CD gas-releasing agents in elementary school classrooms could be linked to lower COVID-19 infections in students.

The strength of this study is that it was a relatively large survey of many public elementary schools in the city. However, this study has several limitations. First, chlorine dioxide-releasing agents were distributed only to elementary schools that requested them, which may have biased the characteristics of the target population. Second, we did not have access to information from elementary schools located outside urban areas. Therefore, caution should be exercised when generalizing the results of this study. Moreover, the odds ratio could not be adjusted for confounding factors. Third, the route of infection was not considered. Hence, future randomized controlled trials should be conducted to evaluate the efficacy of CD gas-releasing agents against COVID-19.

V. Conclusion

A retrospective study in an urban elementary schools in Japan suggested that the use of chlorine dioxide gas-releasing agents may be linked to the reduced development of COVID-19 infections. Further studies are needed to prove a causal relationship.

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We are appreciative to the elementary school officials and the school board for providing the data for this study.

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Abbreviations

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 19; CD, chlorine dioxide.

Conflict of Interest

Yoshinori Kubo, Takanori Miura, Norio Ogata, Jo Shibata, and Takashi Shibata received a salary from Taiko Pharmaceutical Co., Ltd., which manufactures the chlorine dioxide gas-releasing agents (Cleverin®) used in this study. Yoshinori Kubo, Takanori Miura, Kaoru Obinata, Ken Hisata, Mitsuyoshi Suzuki, Eisuke Inage, Naotake Yanagisawa, Jo Shibata, Takashi Shibata, Toshiaki Shimizu belong to the Department of Mass Infection Prevention, which is funded by Taiko Pharmaceutical Co., Ltd.

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Table 1: Characteristics

Chlorine dioxide releasing agent	Number of Elementary Schools	Number of students per elementary school			
		Total	Median	25th	75th
Not used	68	34,810	466	279	668
Used	96	38,714	332	236	526

Table 2: Odds ratio for incident COVID-19

CD gas-releasing agent	COVID-19		Odds ratio	95%CI	*p*-value
	Number of Incidences	Number of Controls			
Not used	4,787	30,023	Reference	-	
Used	5,019	33,695	0.934	0.895-0.975	0.0017

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A Cancer Prevention and Treatment Opportunity

By Vladimir N. Pak

Abstract- Cancer disease results from mutations leading to apoptosis failure and immune system dysfunction. Because one in two people in developed counties will be diagnosed with cancer in their lifetimes, cancer and metastasis prevention should be ahead of therapies. The immune system in cancer patients is compromised and can be fixed with a reboot. The major oncofetal protein – alpha-fetoprotein – can deliver toxins instead of nutrients to the immune suppressor cells and kill them. The death of myeloid suppressor cells unleashes the immune attack on cancer cells, cancer stem cells, and metastases. Injectable and oral formulations of alpha-fetoprotein with toxins provide an opportunity to prevent and treat the disease.

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"The scientific man does not aim at an immediate result. He does not expect that his advanced ideas will be readily taken up. His work is like that of the planter—for the future. His duty is to lay the foundation for those who are to come and point the way."

Nikola Tesla

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I. Introduction

Surgery, radiation, and chemotherapy can cure about half of cancer patients; nevertheless, in the United States alone, nearly 600,000 people died last year. The US cancer death rate has fallen 33% since 1991, partly due to advances in treatment, early detection, and less smoking [1]. It is better to prevent cancer before than to cure the disease after. A healthy environment and lifestyle can prevent only 29% of cancer-causing mutations [2], while everyone needs cancer prophylactics. Each day apoptosis and the immune system erase billions of mutants and expired cells. The immune system is confused in cancer patients. There is an opportunity to prevent early-stage cancer or metastases by rebooting the immune system with a unique delivery vehicle—alpha-fetoprotein (AFP) and toxins.

From the fertilized egg, trillions of cells grow through duplications. Stem cells are deposited on the way. When stimulated to increase, a stem cell is undergoing an "asymmetric division" [3]. The proliferating daughter cell continues to divide and proceed down the tissue hierarchy, from stem cell to progenitor cell, before becoming a fully differentiated mature tissue cell. Multiple types of stem cells have been identified in a wide range of tissue, sharing multipotency characteristics.

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In the bone marrow, hematopoietic stem cells (HSC) exist undifferentiated. They are at the peak of a blood cell differentiation hierarchy. The white blood cell ratio is neutrophils (70%)> lymphocytes> monocytes> eosinophils> basophils. Myeloid-derived suppressor cells (MDSCs) are a small heterogeneous cell population of immature myeloid progenitors of granulocytes, macrophages, and dendritic cells (DCs) at different stages of differentiation generated from a common HSC [4].

MDSCs can leave the bone marrow and spread throughout the body, becoming immune response calmers during pregnancy, cancer, regeneration, stress, autoimmune and infectious diseases, obesity, age, etc.[5]. Besides the bone marrow, other sites generate MDSCs: the placenta and umbilical cord, the tumor site, and the spleen [6].

MDSCs exist in an undifferentiated state at the peak of the immune cell's hierarchy. They affect innate and adaptive immunity cells directly and indirectly. MDSCs inhibit natural killer (NK) cells, DCs, and T-cells, induce regulatory T cells (T regs) and modulate macrophages, etc. [7-9].

In 1862 Rudolf Virchow was the first to link the origin of cancers from otherwise normal cells correctly: "every cell arises from another cell." Indeed, 5% of tumor-causing mutations are inherited, and tumor cells are activated later in life, while 66% of tumor-causing mutations appear during duplications [2]. According to the hierarchical model, the tumor grows from a single cell. Like in embryogenesis, a core group of stem cells exists at the top of the tumor hierarchy, from which other more differentiated cells are formed. Descending from the undifferentiated cells to the most mature cells that comprise the bulk of the tumor mass. Cancer stem cells (CSCs) are cancer cells with characteristics associated with normal stem cells; specifically, give rise to all cell types found in a particular cancer sample. Approximately 73% of current CSC surface markers appear on embryonic or adult stem cells and are rarely expressed on normal tissue cells. It is believed that the elimination of CSCs could eradicate whole cancer [10].

Pregnancy is a natural phenomenon that ensures the survival of the species. An embryo turns off a critical pathway required for the immune system to attack intruders. The suppression of the immune response in pregnancy is robust since the embryo cells have half the father's proteins that the mother's immune system should recognize as foreign. Moreover, even surrogate motherhood is possible, with no genetic

relationship to the embryo. The immunology of pregnancy and cancer is similar [11]. Embryo and cancer cells exploit the mechanisms that allow them to grow despite the host's immune system attacks. During pregnancy, the mother's anti-embryo immune response is neutralized by the oncofetal proteins that re-appear during cancer development.

Some of the oncofetal proteins are AFP, AFP receptor (AFPR), human chorionic gonadotropin (HCG), carcinoembryonic antigen (CAE), and pregnancy-associated protein A. A few molecules regulate the immune tolerance of the mother – AFP, HCG, glycodelin, and pregnancy-specific β1-glycoprotein [12]. Cancers express oncofetal proteins at "a wrong time in a wrong place" to withstand immune system attacks.

Forty years ago, oncofetal proteins were used for cancer patients' vaccination. The placenta is the first organ that forms after conceiving—before any baby's organs even take shape. Immunotherapy with placental proteins has demonstrated a 77.1% 5-year survival rate and a 65.4% 10-year in 35 terminal patients [11]. (The handful of cancer immunotherapy drugs available today have demonstrated robust and durable results only in a minority of patients).

AFP is the major oncofetal protein secreted in early post-implantation embryos of mammals; the ability to synthesize AFP is restricted to the visceral endoderm cells around the embryonic region of the egg cylinder [13]. Later in development, AFP is produced by the yolk sac, liver, and gastrointestinal tract and penetrates the mother's blood (<200 ng/ml)(Fig. 1).

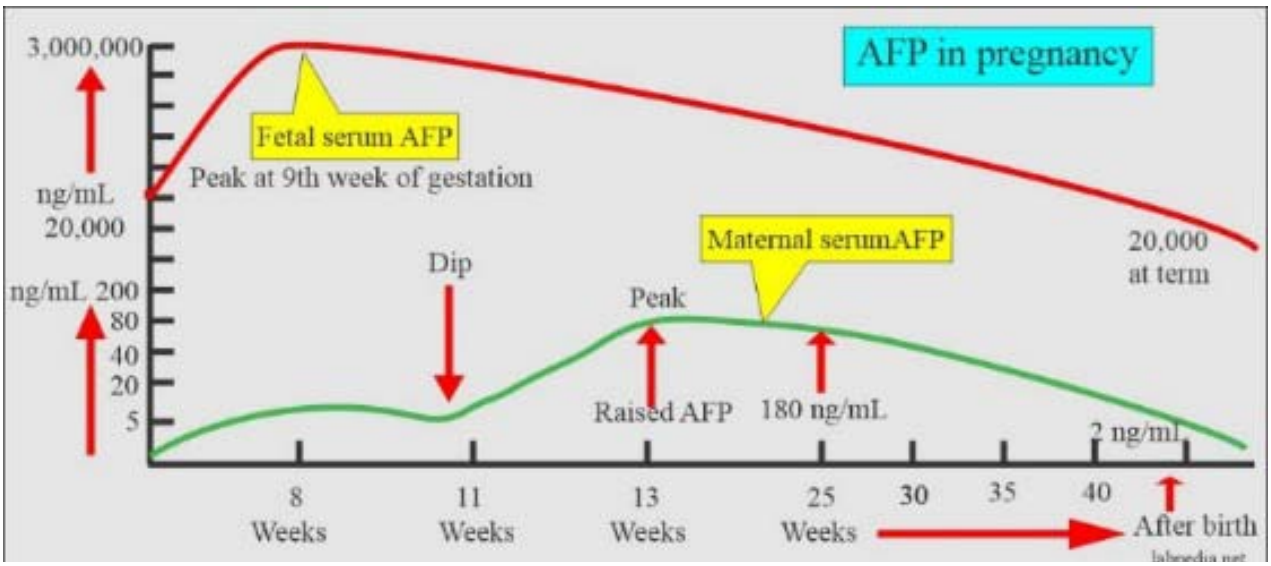

Figure 1: AFP generated by embryo cells penetrates the mother's blood.

AFP can be re-expressed in adult life in a few cancers: hepatomas, germ cell tumors, yolk sac tumors of the ovary, and gastrointestinal cancers. The AFP structure, functions, and clinical applications are well covered in the literature [14-18].

AFP and its peptides have immunomodulatory properties [19-21]. For example, AFP selectively induced a rapid downregulation of surface MHC class II antigens in their expression on human monocytes, thereby making embryo/tumor cells "invisible" to the immune system. MHC class II antigens on monocytes are the key molecules in antigen presentation. They differentiate between a self-cell and an "alien" embryo or cancer cell. AFP neither alters the expression of MHC I, CD4, CD18, CD45, and Fc receptors for IgG on the surface of monocytes/macrophages nor affects the functional maturation of the macrophages Fc receptors or the ability to express antibody-dependent cell-mediated cytolytic activity. AFP may, by reducing the antigen-presenting capacity of monocytes/macrophages, function as an essential factor in maintaining a fetal allograft, as well as participate in the downregulation of the entire immune system in cancer [22].

Nevertheless, the primary immune regulatory impact is AFP ligands because AFP delivers dozens of molecules within 3-5 days of its half-life. Moreover, the AFP-binding monocytes play a fundamental role in regulating the immune response.

The AFP's primary function is nutrient delivery in a shuttle manner (like oxygen delivery by hemoglobin). AFP binds different ligands, delivers them to the AFPR-positive cells, and releases them inside the cell compartment with an acidic pH. The 69 kDa AFP can hide 1-2 molecules (<2 kDa) in its hydrophobic cavity [23]. For example, docosahexaenoic acid (DHA) is not synthesized by the mother, who should take essential nutrients with food. AFP grabs DHA from albumin and transports it through the placenta [24]. Polyunsaturated fatty acids are necessary for many purposes, for

example, the myelination of nerve fibers in the fast-growing embryo's brain.

Embryo cells and normal and malignant peripheral monocytes/macrophages use the autocrine AFP/AFPR system for nutrient supply (Fig. 2, A) [25].

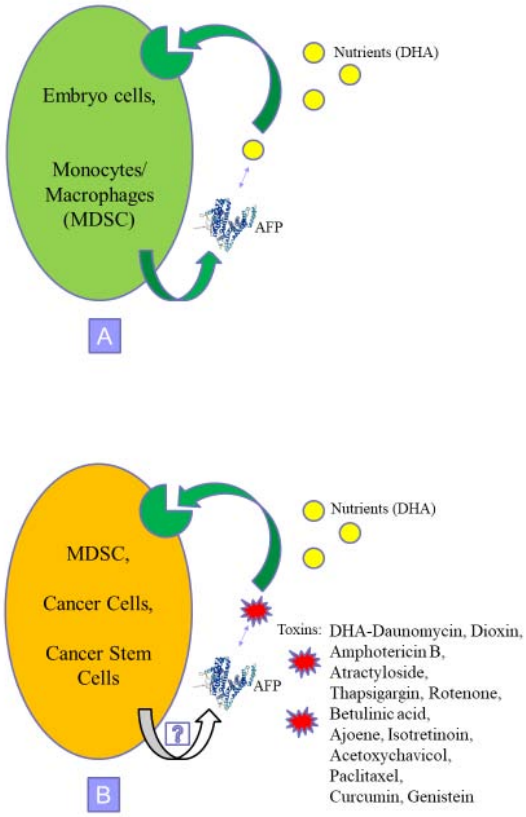

Figure 2: AFP/AFPR shuttle delivery system. A: AFP delivers nutrients to AFPR-positive cells. B: AFP delivers toxins. Abbreviations: AFP – alpha-fetoprotein, DHA – docosahexaenoic acid, MDSC – myeloid-derived suppressor cell, ? – AFP secretion is unknown.

Low-differentiated lymphocytes use AFPR during blast transformation [26]. Monocytes/macrophages have specific 62 and 65 kDa AFP-binding receptors, which are involved in the physiological regulation of the immune response [27].

Unlike AFP, many cancers express AFPR [28], which should be considered the tumor marker and oncofetal protein #1. The AFP gene-knockout rodent models have demonstrated that AFP is not obligatory for full-term delivery [29]. The AFPR gene and structure are unknown yet to perform the gene-knockout experiment. In any case, the AFP/AFPR duo is vital for the embryo (and cancer).

The fact that the mother is tolerable to the embryo for nine months demonstrates that from the very beginning, AFP (Fig. 1) delivers nutrients to MDSCs, "corrupting" them to generate a protective shield over an embryo. MDSCs suppress NK cells which are "spontaneous cytotoxic cells" involved in surveillance against tumor cells. NK cells attack "aliens," low differentiated embryos, stem, cancer cells, and CSCs [30, 31]. NK cells can erase cancer at the earlier stages and solve the urgent problem of metastases.

II. Injectable Afp-toxins

In cancer, MDSCs are "corrupted" also [32]. The effective way to ruin corruption is to eliminate the head. For this purpose, instead of DHA, AFP can deliver toxins to MDSCs (Fig. 2, B). The MDSCs death unleashes NK cells, and the whole immune system, enabling it to recognize and attack cancer the way it does other diseases. In addition, AFP-toxin kills AFPR-positive cancer cells and possibly CSCs (Fig. 2, B).

Like AFP-DHA, AFP complexes with hydrophobic/amphiphilic toxins hidden in the hydrophobic cavity are stable in the bloodstream. They release the toxin only inside the AFPR-positive cells.

After toxin unloading, AFP can work as a shuttle and deliver additional toxins. DHA-daunomycin conjugate binds AFP and inhibits tumor growth in AFP-producing mice [33]. Most cancers do not produce AFP, but >80% are AFPR-positive; hence, exogenous AFP with toxins kills them. Thus, the treatment with AFP and amphotericin B in the excess (1:60-100) for shuttling demonstrated a response in 6 out of 8 cancer patients and increased quality of life [34]. The cytokine storm-like reaction, sometimes observed during the AFP with amphotericin B infusions, preceded cancer cells' death, and it can indicate the consequences of MDSCs death [18]. The potent AFP-binding toxins are expected to provide even better than AFP-amphotericin B response in cancer treatments.

Cancer cells can activate an AFP/AFPR autocrine loop (Fig. 2, B) [35, 36]. MDSCs are progenitor cells with only a few duplication steps from stem and embryo cells, and, as well as CSCs; they should retain an AFP-mediated nutrient delivery system. These need research. At least, AFP is absorbed by MDSCs, stimulating their suppressive activity [37, 38].

AFP attracts MDSCs and T regs through AFP-binding C-C chemokine receptor type 5 (CCR5) [39-41]. These regulatory cells migrate, accumulate, and suppress the immune attack on cancer. Targeting CCR5 reboots immunosuppressive myeloid cells [42, 43].

AFP binds to the neonatal Fc receptor (FcRn) [44, 45]. The FcRn is found in MDSCs in pancreatic cancer monocytes. MDSCs and DCs are elevated in pancreatic cancer patients compared to non-cancer donors [46]. They can be targeted through AFPR and/or FcRn by AFP-toxin drugs.

AFPR, CCR5, and FcRn are valuable MDSCs markers, at least for a transitory period.

Many current drugs do not eliminate CSCs, which may be why many cancers regrow after treatment. Immunotherapy does not act directly on cancer but works on the immune system. Checkpoint inhibitors and CAR T-cells are too unsafe for early-stage cancer; complexity and cost also prevent their application. Dissemination of cancer cells from the primary tumor into distant body tissues and organs is the leading cause of death in cancer patients. While most clinical strategies aim to reduce or impede the growth of the primary tumor, no treatment to eradicate metastatic cancer exists at present [47]. The MDSCs- and CSCs-targeting drugs have a bright future as they are critical in tumor and metastasis prevention [48, 49].

More than 100 years ago, Paul Ehrlich proposed a "magic bullet" that kills cancer cells, sparing the healthy ones. Nevertheless, this approach did not elevate the survival rate of cancer patients. The additional target outside of cancer cells should be hit. This "magic target" is a myeloid suppressor cell. Combining "magic bullets" and the "magic target" approach can cure cancer.

"Magic bullet" can kill "magic target" MDSC. Paclitaxel hits both cancer cells and MDSCs [50], and AFP potentiates its direct cytotoxic and immunotherapy action [51]. Thapsigargin is a more potent toxin than paclitaxel. AFP-thapsigargin complex (ACT-902) depletes MDSCs and tumor-associated macrophages. In mice, chemotherapy using ACT-902 and AFP with paclitaxel demonstrated superior efficacy and safety compared to chemotherapy alone. ACT-902 has led to the complete regression of five out of six highly resistant to chemotherapy POP-92 xenografts by day seven of treatment with no further growth after this period in mice [52]. Or the AFP-maytansine conjugate combines both immunotherapy and targeted chemotherapy with undetectable bone marrow toxicity. It has shown 100% survival with no tumor re-growth after in the mice models [53]. AFP-toxin conjugates might pave a new road to the cancer cure [54-58]. On the other hand, unlike complexes, artificial conjugates have the risk of immune response to themselves.

The neuroblastoma cells may re-express embryonal or fetal antigens, suggesting some reversion towards an earlier stage of differentiation, and they can incorporate AFP [59, 60]. AFP-maytansine conjugate can kill brain tumor cells and CSCs found in human brain tumors [61].

Glioblastoma is the most aggressive, malignant primary brain tumor in adults. Myeloid cells are critical regulators of immune and therapeutic responses to glioblastoma [62]. In the glioblastoma micro-environment, M-MDSCs represent the predominant subset [63]. M-MDSCs can be depleted by AFP-toxin conjugate [54].

It has been found that MDSCs account for approximately 30–50% of the tumor mass in gliomas. MDSCs are increased following conventional chemotherapy treatments [64]. Targeting MDSCs in combination with other therapies has shown promising therapeutic effects in brain cancer [65], and AFP-toxin drugs can be one of these therapies.

III. Oral Instead of Injectable

"Let food be thy medicine, and let medicine be thy food."

Hippocrates

MDSCs can be affected by ingredients from herbs and supplements. For example, withaferin A – a promising anti-cancer constituent of the Ayurvedic medicinal plant *Withania somnifera*–reduces MDSCs function [66]. Nevertheless, pregnant women should avoid *Withania somnifera* tonic as it may induce abortion at high doses [67]. In ancient Rome and Greece, women used silphium, an oral herbal contraceptive. This valuable herb is seen on a coin with a crab that once was a cancer disease name (Fig. 3).

Figure 3: A coin of Magas of Cyrene c. 300–282/75 BC. Reverse: silphium and small crab symbols.

Was silphium used not only for pregnancy prevention but for cancer treatment too? There is no silphium in Nature anymore to check the hypothesis. Still, *Artemisia absinthium*, also used in Roman times for birth control, contains artemisinin that prevents early embryo implantation in animal models. Supposedly, AFP shuttles silphium ingredients or artemisinin to MDSCs, decreases their immunosuppressive activities, and leads to pregnancy or cancer prevention.

AFP wins the competition with excess albumin for binding embryo toxins such as diethylstilbestrol, dioxin, warfarin, etc., and can lead to pregnancy prevention or loss [18]. It can also be true for orally administrated thalidomide, miltefosine, etc. Toxins directly affect embryo cells, and AFP with toxins activate the mother's immune system like paclitaxel.

Traditional medicines and spices often contain anti-cancer agents, such as withaferin A, ajoene, acetoxychavicol, capsaicin, curcumin, quercetin, all-trans retinoic acid, sinigrin, artemisinin, astaxanthin, scutebarbatine A, etc. Small amounts of AFP naturally existing in the body potentiate their anti-cancer activity by the mechanism discussed earlier. To activate the immune system significantly, AFP-binding anti-cancer agents should be used together with exogenous AFP [68, 69].

Porcine AFP and betulinic acid (1:2) gavage inhibited mouse tumor growth. Tumor inhibition was potentiated by the excess of betulinic acid [70]. The beneficial effect of an extra amount of agent for tumor growth inhibition was supported by the experiment with the porcine AFP-ajoene (1:2) complex and ajoene in excess [18].

In suboptimal doses, the oral porcine AFP-atractyloside (1:2) complex has shown a response in six of twelve metastatic colorectal cancer patients [71]. Additional spices, herbs, or supplements having anti-cancer properties could potentiate the treatment. In another trial, a woman with stage IV ovarian cancer took elevated doses of the porcine AFP-atractyloside complex and survived over ten years [18].

AFP-toxin complex absorption from the gastrointestinal tract into the lymph nodes needs research. It can be like IgG-antigen complex absorption through the FcRn of the gut enterocytes [18].

AFP with AFP-binding toxins promises helpful in disease prevention, as they require low concentrations of AFP and toxins, like pregnancy prevention. Injectable recombinant AFP is safe in doses higher than in pregnant mothers' blood (0.3 – 0.5 μg/mL) [72]. Porcine AFP can be taken orally in high doses safely.

IV. Conclusion

AFP-toxin conjugates or AFP with AFP-binding toxins injections deplete MDSCs, reboot the immune system, and can prevent or treat cancer and metastases. As a shuttle delivery vehicle, AFP can potentiate the anti-cancer activity of the AFP-binding toxins or drugs. Oral administration of AFP with herbs or supplements with anti-cancer properties is possible. Like embryo toxins do not hurt the mother but prevent pregnancy, the simultaneous presence of AFP and AFP-binding toxins in the bloodstream can safely prevent early-stage cancers or metastases. Oral preparations do not need high AFP purity, and porcine AFP can be used instead of human protein. Taken once or twice a year course, AFP with AFP-binding toxins can reboot the immune system and prevent cancer and metastasis.

No conflict of interests

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Cancer Stem Cells as the Key to Cancer: Special Emphasis on Prostate Cancer

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Abstract- Recent research into cancer stem cells has refined our knowledge of the origins, maintenance, and progression of cancer. The characteristics of tumor initiating cells and the stem-like properties of tumor side populations that appear to be responsible for tumor maintenance and metastasis have given insights into potential targets for the elimination of treatment-resistant and residual tumor cells. These insights have also provided inroads to understanding and preventing invasive and metastatic progression of cancer. In this review, we discuss recent advancements in understanding of tumor initiating cells and cancer stem cells and their implications on cancer pathobiology and treatment. The role of tumor initiating cell phenotypes on routes of metastasis and the use of stemness markers to guide prognosis and treatment are also discussed. Particular emphasis sections are included that focus on the role of stemness in the pathobiology and treatment of prostate cancer. Of particular interest is the correlation of stemness with decreased androgen receptor expression and resistance to anti-androgen therapy. The overview provided herein represents a primer for the understanding of current knowledge regarding cancer stem cells and their clinical implications in prostate and other cancer types.

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Abstract- Recent research into cancer stem cells has refined our knowledge of the origins, maintenance, and progression of cancer. The characteristics of tumor initiating cells and the stem-like properties of tumor side populations that appear to be responsible for tumor maintenance and metastasis have given insights into potential targets for the elimination of treatment-resistant and residual tumor cells. These insights have also provided inroads to understanding and preventing invasive and metastatic progression of cancer. In this review, we discuss recent advancements in understanding of tumor initiating cells and cancer stem cells and their implications on cancer pathobiology and treatment. The role of tumor initiating cell phenotypes on routes of metastasis and the use of stemness markers to guide prognosis and treatment are also discussed. Particular emphasis sections are included that focus on the role of stemness in the pathobiology and treatment of prostate cancer. Of particular interest is the correlation of stemness with decreased androgen receptor expression and resistance to anti-androgen therapy. The overview provided herein represents a primer for the understanding of current knowledge regarding cancer stem cells and their clinical implications in prostate and other cancer types.

I. Introduction

Despite the significant advancements in cancer therapy throughout the years, cancer remains the most common cause of death worldwide [1]. Knowledge of how cancer initiates and the cellular and molecular origins of cancer continue to grow and be refined. Cancers have been thought to be monoclonal, meaning that each primary tumor originated from a single mutated cell. Mutation in one of a variety of genes may cause cells to form a tumor, while three to seven mutations and/or chromosomal defects may be needed for the development of cancer[2]. Accumulation of mutations can occur over time leading to cancer[2]. Complicating the monoclonal view of cancer, cancer growth and development are impacted by tumor heterogeneity and cell fusion. Recent research has shown that tumor cells and lymphocytes can merge, resulting in phenotypic and genotypic variation in tumor cells [3].

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A population of self-renewing cells with a high tumorigenic potential has been identified in many cancers, which are known as cancer stem cells (CSCs). The continuous and uncontrolled development of malignant tumors is thought to be caused by CSCs, which are also known as cancer-initiating cells (CICs)[2]. These cells are also thought to have a crucial role in metastasis and recurrence[2]. Many theories have suggested that the events occurring in either stem or differentiated cells, such as genomic instability, an inflammatory environment, genetic recombination, and lateral genetic transformation should be taken into consideration as potential CSC origins [2]. The ability of cancer cells to proliferate and, in many circumstances, survive is dependent on underlying stemness[4]. Moreover, due to cancer stem cells' capacity to trigger tumor growth, self-renewal, and multi-drug resistance, the majority of recent cancer research has focused on determining their distinctive characteristics and origins. CSCs have been identified in a variety of tumor types, including head and neck, stomach, breast, pancreatic, lung, liver, colon, melanoma, and bladder cancers[1].

Epithelial-to-mesenchymal transition (EMT) is a strictly controlled process that is essential for the development of tumors. EMT increases cancer cells' ability to migrate and invade and has a direct impact on the production of stem cell-like tumor-initiating cells. TGF-β1 plays crucial roles in the development of tumors and is a critical transcription factor regulating EMT [9]. Undoubtedly, all cells require energy for survival, proliferation, and cell growth. CSCs have a distinct metabolic flexibility in comparison to normal stem cells and significantly rely on oxidative phosphorylation (OXPHOS) as their main source of energy in contrast to non-CSCs, which are primarily glycolytic[5]. In the presence of oxygen, CSCs can alternate between OXPHOS and glycolysis to maintain homeostasis and consequently support tumor development [10].

The inner cell mass of the preimplantation blastocyst is a source of Embryonic Stem Cells (ESCs), which are distinguished and characterized by their pluripotency (the capacity and ability to differentiate into all derivatives of the three basic germ layers: ectoderm, endoderm, and mesoderm) and their potential to self-replicate without limit[6]. Apart from this, understanding originating cell types of cancer is a crucial step in determining mechanisms of tumor initiation and

maintenance. Long-term studies have related the development of prostate glands to stem cells. Prostate cancer is the second most prevalent cause of cancer-related death for men in the developed world , which is the most commonly diagnosed malignancy in males[7]. Regression of the prostate occurs following androgen deprivation, but regeneration occurs after testosterone replacement[8]. The cells responsible for this are located in the proximal ducts and basal layer of the prostate. Numerous characteristics of prostate cancer indicate a stem cell origin[8]. Surgery, radiation, hormonal ablation, and chemotherapy are examples of traditional anti-pancreas cancer treatments. For individuals with severe and/or metastatic cancer, these treatments are ineffective despite increased attempts. Nevertheless, cancer treatments frequently fail because of residual tumor cells that survive therapy, which causes the reappearance of the disease [7]. It has been suggested that CSCs represent this residual population. The general findings reported in the literature illustrate the connection between stem cells and prostate cancer, its therapies, the latest research on cancer stem cells, and potential future technologies to overcome it, which are discussed herein.

II. Stem Cells in Tumor Initiation, Tumor Cell Sustainability and Progression

As stated in Afify and Seno (2019), "Cancer stem cells (CSCs), also known as cancer-initiating cells (CIC), are responsible for the sustained and uncontrolled growth of malignant tumors and are proposed to play significant roles in metastasis and recurrence."[2] The authors clearly state that the initiation of cancer arises from stem cells. Furthermore, this statement is backed by research that was conducted by Mei et al. (2019), who presented very convincing evidence that CSCs have a substantial role in initiation of cancer[9]. This evidence shows that while there is a good understanding of how cancer cells form, the ability to prevent this from occurring remains elusive[10].

A plethora of research has been conducted that strongly supports the role that prostate cancer stem cells (PCSCs) play in the initiation of prostate cancer [9]. This drives the hypothesis that prostate stem cells are targets for prostate cancer initiation. Furthermore, it was proven by Eder et al. (2016) that cancer-associated fibroblasts (CAFs) and prostate cancer cells interact, which allows prostate cancer to proliferate and spread throughout the body [11]. Additional research by Begum et al. (2019) further supports this view [12]. They found that cancer-associated fibroblasts promoted CSC frequency, self-renewal, and metastasis in models of pancreatic ductal adenocarcinoma.

III. Inverse Correlation of Androgen Receptor Expression with Stemness in Prostate Cancer

Cancer progression is defined by continuous loss of a specific phenotype and the growth of progenitor and stem cell features[13]. In prostate cancer, androgen receptor (AR) signaling is important for the development of cancer and therapy resistance. AR signaling is decreased at the transcriptional level in high-grade versus low-grade prostate cancer. Resistance to androgen receptor therapy may be accompanied by loss of androgen receptor signaling and gain of stemness since loss of AR expression is associated with the development of stem cell-like features[13]. One way to inhibit AR signaling is by using the AR antagonist enzalutamide, which is one of the main treatments used for men with castration-resistant prostate cancer[14]. Furthermore, MDM2, an E3 ligase, allows for the ubiquitination of AR in CSCs, decreasing total AR protein levels[15]. The loss of MDM2 allows for the accumulation of AR leading to differentiation into luminal cells and cell death[15]. Blocking MDM2-mediated activity in concert with AR-targeted therapy can provide an approach for eliminating AR-negative CSCs in addition to AR-positive prostate cancer cells, which in turn decreases metastatic tumor burden and inhibits therapeutic resistance [15]. A study on the effects of AR demonstrated the influence of AR on the expression of CD44 and SOX2[16]. The experiment consisted of expressing AR in PC3 cells that are AR-negative. The expression levels of CD44 and SOX2 were decreased, indicating that AR-signaling can reduce stemness characteristics of these cells.

IV. Role of Stem Cells in Tumor Progression

Numerous studies have introduced discrete identities of cells that have stem cell-like features and experience shifts to adapt to a changing microenvironment as the disease progresses. A tumor's cell-of-origin determines its characteristics, such as metastasis, drug resistance, heterogeneity, and immortality[17]. A tumor that originated from cancer stem cells arising late in the life of tumors will have limited metastatic ability, a homogenous phenotype, and a restricted chemokine-receptor profile[17]. Conversely, buildup of mutations in early stem cells can produce tumors with increased rates of metastasis that are driven by a heterogeneous collection of chemokine receptors[17]. The aggressive nature of tumors is dependent on the processes of tissue formation and differentiation that are applied in the early embryonic stages. For example, ectoderm and endoderm-derived tumors metastasize through thelymphatics, while

mesenchyme-derived tumors metastasize by hematogenous spread[17].

CSCs exhibit high plasticity, meaning that they can change their phenotype and their appearance. These changes can be caused by chemotherapy, radiotherapeutics, senescence, and resulting changes in the tumor microenvironment (TME) [17]. Senescence can have anti-tumor effects but can also have negative effects, such as the promotion of cancer stemness, which can in turn increase plasticity, leading to tumor relapse or metastasis [17], [18]. Recent studies have indicated the importance and urgency of diagnostic screening of the TME prior to and during treatment since therapeutic efficacy and adverse effects of anti-cancer drugs can be affected by the TME [19].

In recent years, studies have provided more evidence that cancer stem cells play a pivotal role in the regulation of the TME and immunotherapeutic response in HCC patients. Recent construction of an HCC stemness subtype classifier may offer insights into the interaction between CSCs and the TME and may also be an approach for selecting immunotherapeutic responders in the future[20].

The JAK/STAT3 signaling pathway has a significant role in different types of cancers. Its activation increases metastatic and tumorigenic capability and chemoresistance in cancer by enhancing epithelial-mesenchymal transition EMT, which is related to stemness[21]. EMT is a critical regulator of cancer progression, regulating cancer spread, invasion, and survival[21]. Once activated,STAT3 enters the nucleus through importin-β1 and allows expression of genes that promote pathways that are critical for cancer survival[21].

V. Cancer Stem Cells and Prostate Cancer Survival

A comprehensive study by Tsudenomi et al (2019) concluded that there is no obvious link between CSCs and a patient's ability to survive; however, it is an integral part of establishing a prognosis [22]. Conversely, another study by Yi et al. (2020) effectively proved that prognosis and CSCs have a more direct correlation than previously discussed[23]. Specifically, an experiment was conducted by Li et al. (2020) that showed "that B7-H4 is a potential PCa [prostate cancer] stemness-associated biomarker to predict the prognosis of PCa."[24] This means that the B7-H4 gene is a stem cell-related gene, the overexpression of which can cause tumors to grow, thus establishing a link between CSCs and poor prognosis.

VI. Stem Cell Markers

Over the years, biomarkers have been gaining attention, especially because they are used in diagnosis, therapy, and prognosis, mostly in cancer patients. Cancer stems cells have been known to drive tumor initiation and relapse[25]. Cancer stem cells originate from either differentiated cells or adult tissue resident stem cells. Their importance in disease and development has led to investigation and discovery of stem cell biomarkers. In order to identify CSCs and distinguish them from non-CSC cancer cells, a variety of markers have been used. Common markers are CD133, CD44, IL-6R, and ALDH[26], [27]. These markers, which are predominantly expressed on stem-like cells, correlate with apoptosis resistance and tumor cell growth as they are prevalent on CSCs with enhanced cellular survival phenotypes[28].

Genomic stemness-regulating regions have been investigated for use as a marker for stemness, such as the ERG + 85 enhancer region for leukemia stem cells [29].The use of a reporter to sort an ERG + 85^{High} fraction of acute myelogenous leukemia cells showed the ability of this population to reconstitute the original tumor heterogeneity and was used to identify a 4-Hydroxyphenyl retinamide as an inhibitor of leukemia stem cells. This demonstrates the use of CSC markers to drive drug targeting[29].

VII. Effects of CSCs on Anti-cancer Therapy

a) Correlation of Stemness with Therapy Resistance

CSCs are more resistant to traditional therapies than other tumor cells and can adapt quickly to changes in the microenvironment. Radiotherapy, chemotherapy, or the cessation of treatment can trigger CSC resistance[30]. Tumorcell stemness has been associated with immune checkpoint inhibitor (ICI) resistance. A recent study used RNA sequencing to identify a pan-cancer signature corresponding to the stem.sig stemness-associated gene list that was predictive of ICI immunotherapy response[31]. Using CRISPR datasets, a list of genes involved in stemness whose knockout resulted in enhanced tumor immune response was generated. This evidence indicated that cancer stemness is associated with immunotherapy resistance and provided a genetic stemness profile that may potentially predict immunotherapy response[32].

VIII. Mechanisms of Drug Resistance in Cancer Stem Cells

The mechanisms that protect CSCs from chemotherapy or radiotherapy are an area of ongoing investigation. Recently, emphasis has centered on the role of the DNA damage response (DDR) in the development of tumors. It has been reported that cancer metastasis may be facilitated by an enhanced DDR that shields CSC and chemoresistant cells from the genotoxic pressure of chemotherapeutic medicines or radiation[33].

CSC populations are thought to drive chemoresistance and cancer relapse because of the capacity to self-renew and specialize into a variety of cancer cell lineages in response to chemotherapeutic drugs. Additionally, CSCs have the capacity enter a quiescent non-proliferative state, which supports their capacity to resist chemo- and radio-therapy[33]. Commonly used chemotherapy drugs induce apoptosis in dividing cells. Although effective cancer treatments kill most growing tumor cells, some CSCs survive because of decreased proliferation and chemoresistance and can initiate a relapse [25].

Special Emphasis: Implications of CSCs on Anti-Androgen Therapy Response

Male patients with castration-resistant prostate cancer (CRPC) have the option of treatment with the androgen receptor (AR) antagonist enzalutamide [14]. However, there area significant number of patients that do not respond to the treatment, and the causes behind this resistance are mostly unknown. Research by Alumkal et al. (2020) showed that those with enzalutamide resistance should be enrolled in clinical studies to collect tissue biopsies and apply medications to overcome resistance [14]. Menssouri et al. (2021) posited that AR resistance is related to multiple transcriptional processes that were previously active in pre-treatment samples[34]. O'Reilly et al. (2019) showed that CSCs and tumor relapse are connected on many levels. Also, hypoxic conditions that result from AR resistance cause a variety of signaling pathways to be activated, which elevates stem cell markers and promotes prostate CSC proliferation[35]. Thus, targeting hypoxic signaling pathways might prevent stem cell appearance and lessen resistance. Androgen deprivation therapy resistance has been found to be facilitated by increased expression of Fra1 and PTTG1, which is induced by STAT3 binding to their promoters[21]. Similarly, the stemness of glioblastoma cells is maintained when RTVP1 expression is promoted by the binding of both C/EBPβ and STAT3 to the RTVP-1 promoter, which is linked to poor clinical outcomes[21]. These findings open the door to a more thorough comprehension of the significance of CSC in castration-resistant prostate cancer and resistance to AR antagonism with enzalutamide[36].

Recently, cell plasticity has become a target for therapy in prostate cancer. Tumor cells may transform into a distinct subtypes in response to anticancer therapy, such as the neuroendocrine phenotype, which is linked to treatment failure [37]. Sánchez et al. (2020) proposed a new mechanism for the plasticity of prostate cancervia AMP protein kinase[37]. Prostate cancer cells showed signs of neuroendocrine morphology and expressed more neuroendocrine markers and neuron-specific enolase, which was correlated with increased expression of stem cell markers and resistance to AR [37]. In stem-like cells, overexpression of AMPK reduced the expression of stem markers and hypoxia-inducible factor (HIF-1). Also, docetaxel sensitivity was restored in stem-like AMPK-transfected cells [37].

IX. Stemness as a Therapeutic Target

a) Sensitizing cancer stem cells to cytotoxic therapy/radiation

One promising method for sensitizing breast cancer stem cells (BCSCs) to cytotoxic therapy is targeting the Fbxw7 gene, which maintains cell dormancy. Inhibition of Fbxw7 stimulates BCSCs to progress from the G0 quiescence phase can sensitize these CSCs to current therapies [38], [39]. The antirheumatic drug, sulfasalazine, has also shown to be effective in achieving therapy success by making CSCs more sensitive to radiation [38]. Targeting ATM signaling using an ATM inhibitor is able to resensitizeCD44+/CD24− BCSCs to radiation [38]. Similarly, inhibition of ATM/ATR signaling and downstream targets such as PARP1 and Wee1 increased the sensitivity of CSCs of multiple cancer types to chemotherapy and radiation [40]. Moreover, the promotion of BCSCs development by HIF-1α in hypoxic conditions can be targeted using ganetespib (a second-generation HSP90 and HIF-1α inhibitor)to sensitize BCSCs to chemotherapy in vivo and in vitro [38]. In addition, sequential treatment of patient-derived colorectal cancer xenografts with 5-fluorouracil (5-FU) or chemoradiotherapy (CRT) followed by evofosfamide (a hypoxia-activated prodrug) inhibited tumor growth and decreased the colorectal cancer initiating cell fraction [41]. Furthermore, Croker et al. showed that the inhibition of ALDH activity by using ALDH inhibitors, such as all-trans retinoic acid (ATRA) and diethylaminobenzaldehyde (DEAB), can make TNBC cells more sensitiveto chemotherapy and radiotherapy [42]. Similarly, silencing ALDH gene expression in ALDH-expressing ovarian CSCs reverses chemoresistance in these cells [43].

Another method for sensitizing CSCs is by targeting NOTCH signaling, which has been shown to sensitize patient-derived glioma stem cells to radiotherapy in vitro and to prevent xenograft formation [44]. In addition, inhibiting WNT/β-catenin pathway by using imatinib, a c-KIT/CD117 inhibitor, or anti-CD117 siRNA can reverse chemoresistance [45]–[48]. This was shown in pre-clinical models where the number of cancer stem cells decreased in squamous cell carcinoma and breast cancer xenografts, allowing therapeutic resistance to be overcome [48]–[50][. Nanotechnology has offered a novel way to target CSCs by enhancing local drug delivery. For example, PEGylated gold nanoparticles fused with anti-CD44 antibody greatly enhanced the targeting of breast and gastric cancer stem cells [51], [52]. In addition, using

carbon nanoparticle-mediated hyperthermia allows heating of cancer stem cells to overcome resistance by generating intense localized heat inside these cells which can reach temperatures above 50 ◦C [53]. Finally, Hh-activated CAF targeting in patient-derived xenografts using smoothened inhibitors (SMOi) can inhibit FGF signaling to suppress CSC populations and overcome chemoresistance [54].

b) Targeted therapy directed toward cancer stem cells

Disrupting CAF-CSC crosstalk is an attractive approach to targeting CSCs. Using Stattic, a STAT3 inhibitor, to block IL-6/IL-6R/STAT3 signaling can reduce stemness of BCSCs [55]. Additionally, the STAT3 antisense oligonucleotide AZD9150 exhibits antitumor tumor activity in refractory lymphoma and NSCLC clinical trials [54]. Further, CCL2-neutralizing antibodies and inhibitors of α- and γ-secretases that activate NOTCH have reduced stemness and stopped metastasis of breast cancer cells and glioblastoma cells in preclinical studies [57], [58]. Moreover, using AMD3100 (plerixafor) to block SDF-1/CXCR4 signaling greatly suppresses the CSC population in breast, colon and renal cancers[59]–[61]. However, these interventions have been relatively ineffective in patients with solid tumors [60]–[63]. On the other hand, using BKM120 or Ly294002 to block PI3K/AKT signaling can kill CSCs in can kill colon, prostate and breast cancers [66]–[69], and the PI3K inhibitors PX-866 [73], alpelisib [74], PQR309 [75] and pictilisib [76] were effective in patients with solid tumors [70]–[73].

LGK974, Wnt-C59, and cyclosporin A, which inhibit the WNT/β-catenin pathway are able to inhibit the proliferation of CSCs in different cancers [74]–[76]. It has also been shown that vismodegib, a Hedgehog inhibitor, inhibits proliferation and triggers apoptosis in breast, colon, and prostate cancers [77]–[79]. Sonidegib, another hedgehog inhibitor, has shown to inhibit CAF activation and reduce the CSC population in triple-negative breast cancer[54]. Another approach is targeting the metabolism of CSCs. One of the most studied strategies that targets metabolism is the use of compounds that block electron transport chain (ETC) complexes, which inhibits mitochondrial respiration[80]. Antidiabetic drugs such as metformin and phenformin can act as ETC inhibitors to impair oxidative phosphorylation in CSCs[80]. In addition, antibiotics like doxycycline, tigecycline and bedaquiline can target mitochondrial translation and biogenesis {cite}. A method for selective drug delivery in mitochondria can be adopted using chemotherapeutics and small drug-conjugated nanocarriers[80]. Targeting lipid metabolism is another pan-CSC strategy. Stearoyl-CoA desaturase 1 (SCD-1) inhibitors have shown to target properties of stemness in cancer models in vitro and in vivo[80]. Statins can also be used to inhibit cholesterol synthesis via the mevalonate pathway[80]. Lipid uptake can be targeted using strategies revolving around inhibition of the transporter CD36 either pharmacologically or using blocking antibodies [80].

Treatment with salinomycin-encapsulated lipid-PLGA nanoparticles conjugated with CD44 antibodies has resulted in improved cytotoxic effects on CD44+ prostate cancer initiating cells with enhanced suppression of tumorsphere formation [81]. Using drugs, antibodies, vaccines, and CAR-T cells to target transcription factors, intracellular signaling pathways such as Hedgehog, Notch, Wnt signaling, extracellular factors, CSC-associated surface markers, apoptotic pathways, and CSC-niche interactions presents several effective ways to target CSCs [39], [82]. Lv et al. showed that vitamin C uptake via sodium-dependent vitamin C transporter 2 (SVCT-2) induced apoptosis in liver cancer stem cells in vitro and in vivo experiments [83]. Furthermore, in a phase II trial, Brown et al. demonstrated that using Metformin as a treatment caused a major reduction in the CSC population, a change in DNA methylation of carcinoma-associated mesenchymal stem cells (CA-MSCs), and elimination of increased chemoresistance caused by CA-MSCs [84].

c) Directing immunotherapy to cancer stem cells

A small number of immunotherapyoptions to target CSCs exist to date and include adaptive T-cells, dendritic cell (DC)-based vaccines, and immune checkpoint inhibitors[85], [86].The discovery of ICIs dramatically changed the standard-of-care practice in oncology allowing for the targeting of tumor immunity. CSCs represent a unique subpopulation of tumor cells that initiate and perpetuate tumors. CSCs are recognized as acore cause of drug resistance, cancer relapse, invasion, and migration. CSC self-renewal and immune evasion can be driven by dysregulated FTO(Fat mass and obesity-associated protein)[87]. FTO has been reported to be upregulated in many tumors[87]. Targeting FTO helps to suppress tumor growth, potentiates immunotherapy, and attenuates drug resistance[87]. Inhibition of FTO can dramatically change immune response by suppressing expression of immune checkpoint genes[87]. It has been reported that two potent small-molecule FTO inhibitors exhibit strong anti-tumor effects in multiple types of cancers[87]. This study was conducted using samples from patients with newly diagnosed, after treatment, or relapsed leukemia. Through a series of screening and validation assays the authors discovered that the FTO inhibitors CS1 and CS2 displayed potent anti-leukemic effects in vitro by selectively suppressing FTO activity and signaling leading to the activation of apoptosis. The potent anti-tumor efficacy and minimal side effects of CS1 and CS2 observed in this study suggest a high potential for clinical application. In addition to hematopoietic malignancies, FTO has also been reported to play oncogenic roles in many types of

solid tumors (glioblastoma, breast cancer, and pancreatic cancer)[87]. This evidence confirms the broad therapeutic potential of immunotherapy targeting CSCs in various types of cancers, particularly FTO inhibitors.

d) Vaccination against CSCs

A growing body of evidence suggests that complete tumor eradication is impossible without effective elimination of cancer stem cells (CSCs). The resistant nature of CSCs makes conventional chemotherapy inefficient. For example, breast cancer stem cells (BCSC) activate molecular pathways that render them resistant to current therapies, such as the increased functionality of DNA-repair mechanisms, the overexpression of detoxifying enzymes, enhanced anti-oxidant capabilities, and resistance to apoptosis [85]. Therefore, targeted immunotherapy using vaccines may be a compelling option [27]. BCSCs possess several mechanisms to evade the immune response, thus use of vaccines for the treatment of chemoresistant breast cancer, perhaps in combination with ICIs, may be an attractive modality. Currently, there are two tumor vaccine options that are being studied: DC (dendritic cell)-based vaccines [86] and vaccines consisting of irradiated induced pluripotent stem cells (iPSC). Both are undergoing clinical trials but have not thus far been approved for targeted immunotherapy for cancer[89].

X. Therapeutic Markers

CSCs express immune resistance markers and exhibit specific immune characteristics in various cancers. This phenomenon can be exploited using immunotherapies to target CSCs [27].A literature review concluded that as a sub population of bulk tumors, CSCs resist conventional cancer therapies, escaping from antitumor immunity through lower expression of immune receptors [89]. This prompts a drive toward the development of smarter, CSC-targeted, therapeutic approaches using specific CSCs markers.

a) Markers for the use of immune checkpoint inhibitors

The development of ICIs marked a new era in anti-cancer therapy. This treatment modality has resulted in favorable responses and substantial improvement in survival in various cancer types. Therefore, increasing attention is being paid to the identification of predictive biomarkers for the efficacy of ICIs. Identifying predictive biomarkers can help to understand whether ICIs will be effective in tumor suppression. Such information can influence decision-making toward individualized anti-tumor immunotherapy and help to monitor drug efficacy and progression of the disease. PD-L1 immune checkpoint ligand has been shown to be expressed highly in CSCs, to contribute to the stemness of these cells, and to mediate immune evasion [89].

XI. Looking Forward

Tumors consist of heterogeneous cell populations. This heterogeneity plays key roles in regulating tumor initiation, metastasis, recurrence, and resistance to anti-tumor therapies [39]. Defining the regulatory mechanisms of heterogeneity is essential for targeting BCSCs and treating breast cancer [90]. A recent study outlines discoveries of novel regulators of BCSCs and their niches for BCSC heterogeneity[54]. In this study, hedgehog signaling in tumor cells led to the reprogramming of cancer-associated fibroblast to support a CSC phenotype that was resistant to chemotherapy. The authors highlight that using this new data allows for better prognosis and prediction of therapeutic efficacy, which may provide novel and more efficient treatment strategies[54].

Hypoxia is a common feature of tumors that presents opportunity for future therapies, developing because of the rapid growth of tumors, outpacing oxygen supply. Hypoxia is affected by blood flow, which is counteracted by formation of abnormal blood vessels ("neo-vessels") supplying the tumor. Tumor hypoxia is associated with the invasion, metastasis, tumor survival, suppression of anti-tumor immunity, and hampered therapeutic response. Several potential mechanisms may play a role in these phenotypes, including alteredgene expression, activation of oncogenes, inactivation of suppressor genes, genomic instability, and clonal selection [90]. A. Emami Nejad et al. studied the effects of hypoxia on tumor biology and possible strategies to manage the hypoxic tumor microenvironment [68]. The authors noted that hypoxia enhances the aggressiveness of tumors and creates a barrier to conventional cancer therapy, including radiotherapy, chemotherapy, and phototherapy, confirming that tumors that are hypoxic are associated with a poorer outcomes[90]. The role of hypoxic CSCs in tumor expansion and malignant progression favoring immune escape has been highlighted[54].

The effects of hypoxia on tumor cells are mediated by hypoxia inducible factors (HIFs). HIFs upregulate the expression of angiogenic factors, particularly VEGF in CSCs, and promote tumor angiogenesis [90]. HIF proteins are master regulators of oxygen homeostasis. Therefore targeting HIFs is an attractive strategy in the treatment of tumors. Several approaches have been identified for targeting hypoxia including, hypoxia-activated prodrugs (HAPs), specific targeting of HIFs, and targeting downstream HIF signaling pathways or critical pathways specific to hypoxic cells (such as mTOR and UPR) [90]. A. EmamiNejad et al. concluded that HIF stabilization in hypoxic tumor cells induces the expression of specific target genes encoding proteins that promote neo-angiogenesis (VEGF), metabolic changes, stemness and metastasis[90]. It has also been noted that effective

anti-angiogenic (VEGF) therapy may be achieved in combination with inhibitors of tumor hypoxic adaptation [54].

XII. Conclusion

In summary, stemness in tumor cells is an indicator of therapeutic resistance and prognosis. Refinement of the markers of stemness used to identify these cells and their phenotypes in cancers is leading to the ability to predict treatment responses and develop new approaches to the effective elimination of resistant tumor cell populations. Better understanding of the nature of cancer stem cells heightens our awareness of the appropriate application of emergent therapy modalities, such as immune checkpoint inhibitors, tumor vaccines, and hypoxia-targeted drugs. Improved understanding of tumor biology is not possible without the intimate understanding of the role of the cancer stem cell as a critical player in the initiation, maintenance, and progression of cancer.

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Inflammatory Markers and Risk Factors in Hypertensive Patients: A Cross-Sectional Study

By Bettanin, Francelise Susan Mihara, Bacci, Marcelo Rodrigues & Fonseca, Fernando Luiz Affonso

Summary- *Objective:* To observe risk factors that hypertensive patients present in the outpatient segment from the nursing perspective care.

Method: Cross-sectional study where essential hypertensives of legal age belonging to the hypertension program of a municipality in Bahia were included. Those with cancer, hepatitis, HIV, lupus, arthritis, pregnant women, and chronic corticosteroid users were excluded. Collected patient demographic information and cardiovascular risk factors.

Results: Included 61 patients with a mean age of 58±11, 56% women. A relationship was established between age/glucose; IL6/LDL; vitamin D/ferritin; waist circumference/BMI; BMI/CRP; smoking, age, blood pressure, LDL, and neutrophil/ lymphocyte ratio. The statistical analysis evaluated predictive variables for developing hypertension and high cardiovascular risk. In the cardiovascular risk stratification, 09 patients had low chance; one was intermediate, 37 high risk, and 02 very high risk.

Keywords: *cardiovascular risk; risk factors; arterial hypertension.*

GJMR-F Classification: *DDC Code: 616.132 LCC Code: RC685.H8*

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Conclusion: Although arterial hypertension has a multifactorial etiology, obesity, smoking, and blood glucose were the risk factors that correlated positively, associated with the studied markers.

Keywords: cardiovascular risk; risk factors; arterial hypertension.

I. Introduction

Hypertension (AH) is directly related to the development of cardiovascular diseases, accounting for 40% of deaths from stroke, 25% of deaths from coronary artery disease, and, in combination with *diabetes mellitus* (DM), 50% of cases of end-stage chronic kidney disease [(1)]. It is a chronic non-transmissible condition characterized by persistent elevation of blood pressure (BP) [(2)]. In Brazil, it is estimated that 35% of the adult population is hypertensive, according to data from the Ministry of Health (MS). Around 50% of the remaining persons do not know they have the disease. Considering only those over 60, this percentage is around 65% of the hypertensive people in the country.

In most cases is asymptomatic, implying the difficulty of early diagnosis and without adherence to the treatment recommended, whether pharmacological or not. For this reason, AH control is still so low, making it a challenge for health services. Associated with the main risk factors such as age, gender and ethnicity, obesity and dyslipidemia, sedentary lifestyle, salt and alcohol intake, and socioeconomic and genetic factors, AH contributes to the worsening of the patient's cardiovascular morbidity and mortality.

Since 2005, ischemic heart disease and cardiovascular disease have been Brazil's leading causes of death. Up to 2015, there was an increase of 18.8% in deaths by the first cause and 13.3% from the second cause. During this period, ischemic heart disease moved from the second to the first cause of premature deaths (below 60 years), with an increase of 8.5%[(3)].

Among these risk factors related to hypertension, some can still promote inflammation, such as dyslipidemia and obesity. The fat tissue is a dynamic organ, the leading storage for primary, excess energy, has an endocrine function, and synthesizes a series of biologically active compounds that regulate metabolic homeostasis [(4)].

The inflammatory profile in obese individuals is called metabolic or meta-inflammation[(5)]. This whole process alters the adipose tissue's functioning, thus characterizing a dysfunctional tissue. Among the characteristics of this dysfunction, the fat mass will present changes in its cellular composition, such as, for example, an increase in the number of inflammatory cells [(4)]. It produces a series of substances, such as macrophages, which, in turn, infiltrate the adipose tissue during the advanced stages of obesity and participate in the inflammatory event by producing more cytokines, such as interleukin-6 (IL-6) [(6, 7)].

Therefore, hypertension, known as a non-communicable disease, imposes the need for the individual to adopt changes in their lifestyle, primarily related to those caused by restrictions resulting from the disease, therapeutic conditions, and clinical controls, as well as the possibility of recurrent hospitalizations [(8)].

Considering that hypertension is a severe public health problem, the importance of this study for health surveillance is highlighted to understand how it can alter the population's quality of life and morbidity and mortality profile.

The objective of this study is to observe the risk factors that a hypertensive population presents in the outpatient segment from the nurse's perspective of care.

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II. Method

a) Design

This is a cross-sectional, analytical study with a quantitative, population-based approach.

The study was conducted in a primary health unit in the municipality of Barreiras in the state of Bahia, in the northeast region of Brazil. The unit is a reference in its area for the diagnosis, treatment, and follow-up of patients with hypertension. The sample was determined based on the patients linked to this health unit using the simple random sampling method. All patients in the hypertensive follow-up program were considered for the study. As the number of hypertensive patients (n) monitored by the health unit was known (70 patients), all were invited to participate in the study. To calculate the sample size a confidence level (z) of 95% was used, a standard deviation (p) of 0.5, and a margin of error (e) of +/- 5%, being estimated 60 participants. Size = $[z^2 xp (1- p)] /e^2/1+[z^2 xp (1-p)]/ e^2 xn$

The inclusion period comprised October 2019 to May 2020, and there was no impact or risk to participants due to the COVID-19 pandemic.

Individuals over 18 and hypertensive patients enrolled in the health unit were included after their written consent. Patients with cancer undergoing treatment in the last five years, the presence of viral hepatitis or HIV infections, rheumatologic diseases such as lupus and rheumatoid arthritis, pregnant women, and chronic users of steroids were not considered for the study.

The demographic information of each patient and the risk factors for a cardiovascular disease they presented were collected. These factors were the presence of dyslipidemia, diabetes, smoking, obesity, sedentary lifestyle, and occurrence of coronary artery disease.

A blood pressure measurement for staging their disease was performed according to the Brazilian Hypertension guideline [2].

The laboratory variables evaluated to determine renal function were serum creatinine, assessed by the modified Jaffé reaction. The estimative of the glomerular filtration rate (eGFR) was performed by the CKD-EPI equation [9, 14].

The identification of chronic kidney disease (CKD) was defined as the eGFR of less than 90 ml/min/1.73m2, according to KDIGO [10].

The Framingham scale was used to measure the cardiovascular risk of each patient [11-13].

Each patient's inflammatory status was assessed by measuring ultra-sensitive C-reactive protein (CRP), interleukin-6 (IL-6), serum ferritin, and serum 25-OH-vitamin D. These parameters were measured by electrochemiluminescence.

b) Statistical Analysis

For the statistical analysis, the SPSS v21.0 software was used. The Kolmogorov-Smirnov test was used to verify the uniformity of the data.

Non-parametric tests were used to allow the analysis of variables with different distributions.

Statistical analyses were sequentially adjusted for the following confounding factors: 1) mean and standard deviation for quantitative variables; 2) percentage for qualitative variables, except for variables describing inflammatory markers, which were described as mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum.

Spearman's correlation analyzed the relationships between quantitative variables, and the chi-square test was used for qualitative variables. A significance level of 0.05 (5%) was defined for this study. A logistic regression model was constructed to evaluate the predictive variables for hypertension and high cardiovascular (CV) risk development.

Regardless of their significance, all quantifiable and non-quantifiable variables were used in the statistical analysis of the studied sample.

The study followed the STROBE systematization for cross-sectional studies.

The study was approved under number 3.286.842, issued by the local ethics committee.

III. Results

Table 1 presents the descriptive data of the characteristics of the sample. Seventy participants were invited to participate in the study, of which 61 answered the call, and all 61 individuals met the inclusion criteria. Thus every participant was included, and no data was lost.

The participants involved in this research had a mean age of 58±11 years, 56% female.

Table 1: Demographic characterization of the sample and cardiovascular risk factors in Barreiras, Bahia, Brazil, 2020

Variables	Participants (n=61)
Age years)	58±11
Weight (Kg)	71.7±13.1
Height (m)	1.6±0.1
Waist circumference (cm)	95.3±9.4

BMI (Kg/m ^{2})		27±5
Sex		
	Male	27 (44.3%)
	Female	34 (55.7%)
Ethnicity		
	Caucasian	6 (9.8%)
	Black	55 (90.2%)
Education		
	None	8 (13.1%)
	Literate	4 (6.6%)
	incomplete 1st grade	20 (32.8%)
	complete 1st degree	10 (16.4%)
	incomplete high school	3 (4.9%)
	complete high school	9 (14.8%)
	Incomplete higher	3 (4.9%)
	Graduated	4 (6.6%)
Consumption of alcohol		
	Yes	12 (19.7%)
	No	49 (80.3%)
Hypertensive therapy		
	None	2 (3.3%)
	Use one medication	19 (31.1%)
	Use two medications	20 (32.8%)
	Use three medications	11 (18%)
	Use more than three medications	9 (14.8%)
Use of drugs		
	Yes	1 (1.6%)
	No	60 (98.4%)
Chronic kidney disease		
	Yes	4 (6.6%)
	No	57 (93.4%)

The characterization of inflammatory markers was described in Table 2 in detail to allow identification of the sample amplitude, as shown in Figure 1.

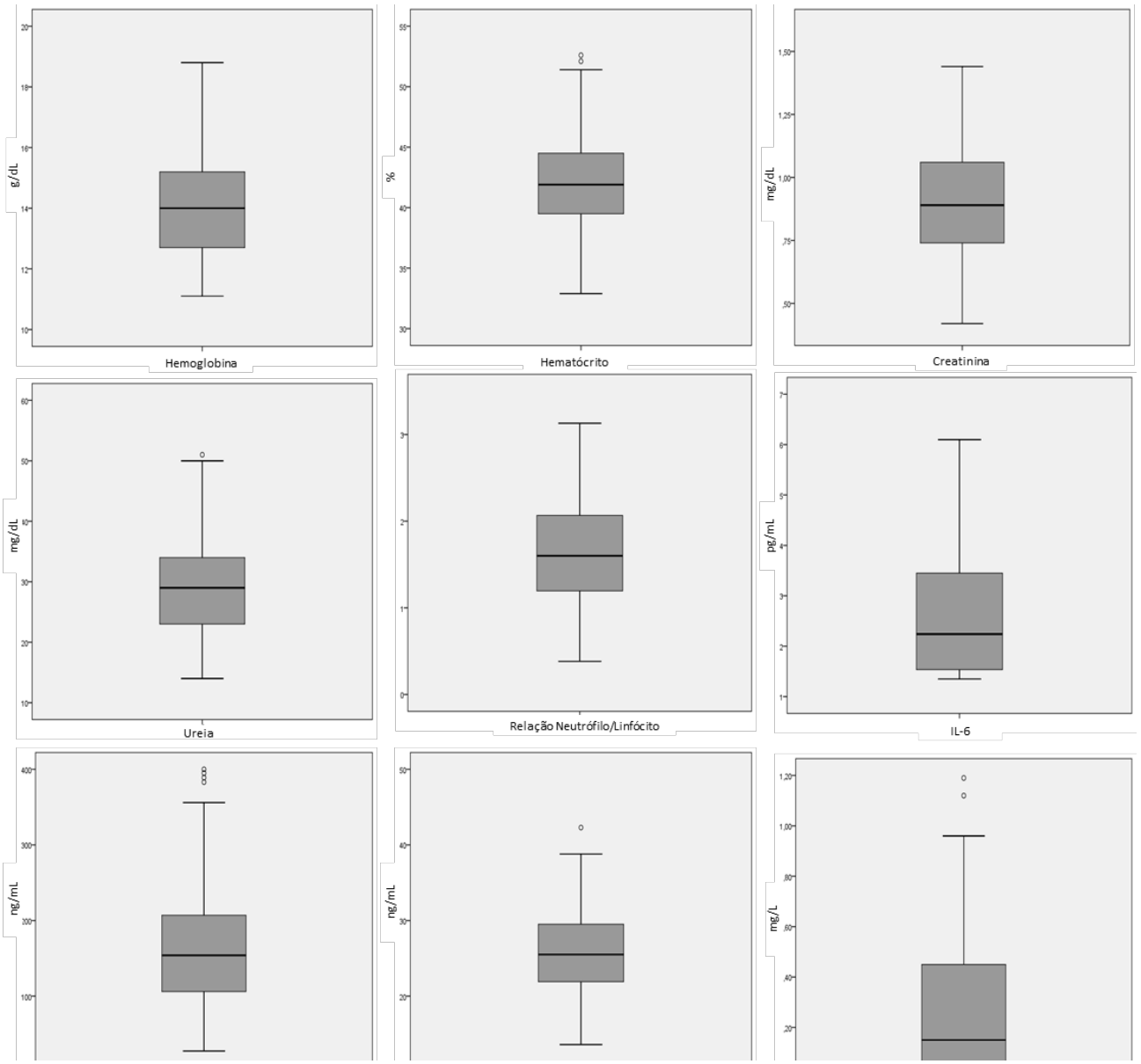
Table 2: Characterization of the laboratory parameters of the population studied in Barreiras, Bahia, Brazil, 2020

	Mean±SD	Median	Percentiles		Minimum	Maximum
			25	75		
Hemoglobin (g/ dL)	14.17 ± 1.69	14	12.70	15.25	11.10	18.80
Hematocrit (%)	42.63 ± 4.63	41.90	39.40	45.30	32.90	52.60
Creatinine (mg/ dL)	0.91 ± 0.25	0.89	0.73	1.08	0.42	1.44
Urea (mg/ dL)	29.3 ± 7.65	29.00	23	34	14	51
Neutrophil/Lymphocyte Ratio	1.67 ± 0.65	1.60	1.18	2.07	0.38	3.13
IL-6 (pg / mL)	2.61 ± 1.17	2.24	1.53	3.56	1.35	6.10
Ferritin (ng / mL)	173.11 ± 99.92	154	99.65	207	27.40	400
D Vitamin (ng / mL)	26.18 ± 6.58	25.50	21.75	29.70	13.60	42.30
CRP (mg/L)	0.28 ± 0.29	0.15	0.06	0.45	0.02	1.19

Standard Deviation (SD); interleukin 6 (IL-6); C-reactive protein (CRP);

When cardiovascular risk (CV) was stratified, 09 patients presented a low risk, 13 patients at intermediate risk, 37 patients with high risk, and 02 patients showed a very high risk in the sample studied.

When calculating the glomerular filtration rate (GFR) in the studied sample, 55.73% (34 patients) had an expected result. In contrast, the others, 44.26% (27 patients), presented an altered result when comparing the parameters age, creatinine, sex, and ethnicity, by the CPK-EPI equation [9, 14].



Grams by deciliter (g/ dL); percentage (%); milligrams by deciliter (mg/ dL); interleukin 6 (IL-6); picogram by milliliters (pg /mL); nanograms by milliliters (ng/mL); C reactive protein (PCR); milligrams by liter (mg/L).

Figure 1: Box diagram for inflammatory marker variables

Table 3 shows the variables that presented correlation when analyzed among themselves. The relationship between age and glucose was direct ($p = 0.008$), while eGFR was inverse ($p < 0.001$). Waist circumference is directly related to both BMI ($p < 0.001$) and CRP ($p = 0.019$), so BMI and CRP are also directly related ($p = 0.001$). An inverse relationship was found between IL-6 and GFR ($p = 0.027$), a direct relationship with CRP ($p = 0.009$), and a direct relationship between Glucose and Ferritin ($p = 0.020$).

Table 3: Relationship between blood variables and age with BMI and waist circumference in Barreiras, Bahia, Brazil, 2020

	Glucose	BMI	GFR	IL6	CRP	Vitamin D
Age						
Correlation Coefficient*	0.339	-0.246	-0.492	0.076	0.088	-0.022
p-value	0.008	0.056	< 0.001	0.581	0.502	0.868
Waist circumference						
Correlation Coefficient*	0.044	0.752	-0.009	0.151	0.300	-0.029
p-value	0.738	< 0.001	0.944	0.272	0.019	0.823
BMI						
Correlation Coefficient*	0.005	-	0.043	0.183	0.421	-0.034
p-value	0.972		0.744	0.181	0.001	0.793
IL6						
Correlation Coefficient*	-0.181	0.183	-0.298	-	0.351	-0.198
p-value	0.191	0.181	0.027		0.009	0.148
Ferritin						
Correlation Coefficient*	0.301	0.005	-0.001	-0.092	-0.096	0.191
p-value	0.020	0.970	0.994	0.503	0.462	0.141

** Spearman correlation coefficient; body mass index (BMI); Glomerular filtration rate (GFR); Interleukin 6 (IL6); C - reactive protein (CRP)*

It is observed that the increase in blood glucose directly influences the increase in cardiovascular risk (p = 0.027), as exemplified in table 4.

Table 4: Association between blood glucose and cardiovascular risk in Barreiras, Bahia, Brazil, 2020

	Normal Glucose	Changed	p-value
Cardiovascular risk			
Low	7 (77.8%)	2 (22.2%)	
Intermediary	6 (50%)	6 (50%)	0.027*
High	11 (28.9%)	27 (71.1%)	
Very high	0 (0%)	2 (100%)	

** Chi-square test.*

IV. Discussion

This study was conducted in the municipality of Barreiras, a medium-sized city in the state of Bahia, 863 km from the capital. It has an area of 7,538 km^2, with an estimated population of 153,831 inhabitants, and is considered the twelfth largest population, economic, political, and cultural center of Bahia [15].

Its population is predominantly non-white and mixed. It is the gateway to health services through primary care or the regional hospital that serves the entire western region of Bahia.

Although abdominal circumference provides independent and additive information to the body mass index (BMI), the hypertensive effect of weight gain was well recorded [2]. Excessive body adiposity, especially visceral adiposity, is a significant risk factor for BP elevation, which may be responsible for 65 to 75% of cases of hypertension [2].

Weight loss reduces BP, even without reaching the desired body weight. For overweight or obese individuals, weight loss is an essential recommendation in treating AH[2]. All participants had a waist circumference above 80 cm in diameter in the sample studied. Those with higher waist circumference also had higher weight and a higher BP, thus confirming that individuals with higher weight also had more elevated BP. In addition to being overweight, the mean BMI (27±5) and waist circumference (95.3±9.4) were above the recommended, corroborating the obesity of the studied population.

However, it was impossible to establish a direct relationship between obesity and a sedentary lifestyle since the frequency of physical exercise practiced by the study participants was not evaluated; only the practice of any physical activity was verified. Nor can a relationship be established with the sex of the patients, although the highest proportion was female (55.7%).

However, the Brazilian Guidelines on Hypertension states there is a relationship between a sedentary lifestyle and hypertension since the lack of physical activity is 27.5%, with a higher prevalence among women (31.7%) than men (23.4%), confirming the profile found in the sample studied [2,16].

Ethnicity is also considered an essential factor for hypertension because non-white individuals are more likely to develop higher cardiovascular risk. Non-white individuals (90.2%) were the majority in the study population, consistent with the ethnicity prevalent in the region [2].

Regarding the education/instruction of the individual, it is associated that the lower level of education can generate limited conditions of absorption of information to people about their health, linking to more illness and negative correlation with the prevention, control of hypertension, and treatment adherence. In the sample, we obtained 32.8% of individuals with incomplete primary education and 13.1% with no education, with a total of 43.9% of people with little or no education, which seems to be a more relevant factor for the differences in the prevalence of hypertension than ethnic implication itself.

In addition to risk factors being predictors of outcomes, hypertensive patients should periodically undergo laboratory tests, and these, when associated with traditional cardiovascular risks, can assist in this stratification. In hypertensive patients, it is also essential to investigate associated comorbidities, especially DM.

According to the Guidelines of the Brazilian Society of Diabetes, fasting glucose levels for non-pregnant adults are considered normal when they vary between 70-99 mg/dL[17]. In the study, 71.1% of the patients in the sample presented glycemic changes, which corroborates directly with the increase in CV risk (60.6%).

Smoking is associated with the development of albuminuria, which may contribute to progressive kidney disease and increased risk of CVD [14,18]. According to the *Dialysis Morbidity and Mortality Study* (DMMS) *Wave* 2, 40% of patients on dialysis are current smokers (16.6%) or former smokers (24.2%) [19]. Smoking has vasoconstrictive, thromboembolic, and direct effects on the vascular endothelium and is a strong predictor of increased serum creatinine levels in non-diabetic patients 65 years of age and older [20, 21].

Among the inflammatory markers is IL-6, a pro-inflammatory cytokine that acts in different tissues, mainly concerning immune and humoral effects, and is released primarily by adipocytes [22-24]. Visceral adipose tissue releases about 15 to 30% of all IL-6 production [23]. This fact strengthens the inclusion of obesity as one of the risk factors for CVD [23].

IL-6 also has effects on carbohydrate and lipid metabolism. As adipose tissue is an essential source of this cytokine, in obese individuals, IL-6, as a potent stimulator of CRP, can inhibit the activity of lipoprotein lipase, causing a low glucose uptake mediated by insulin, increasing insulin resistance, exemplified in table 3, which shows the direct relationship of glycemia and IL-6, as well as CRP[25,26].

The neutrophil/lymphocyte ratio (NLR) can be used as an easy marker of integration into the laboratory routine at virtually no additional cost. There is an increase in NLR when there are inflammatory events [27].

High serum levels of CRP indicate a higher risk of the individual developing coronary and cardiovascular diseases, through the elevation of BP, by hemodynamic, hormonal, and biomechanical mechanisms [28-32]. In the sample, hypertensive patients with higher abdominal circumference and BMI had the highest values of CRP, showing that obesity is directly related to hypertension. A direct relationship was also established between CRP and glycemia and IL-6, reaffirming cardiovascular risk.

On the other hand, Ferritin is associated with the presence of anemia and, in high concentrations, implies iron overload, resulting in oxidative stress, therefore participating in the inflammatory effect. No impact of anemia was detected in the population studied. However, it is considered a non-traditional risk factor in the development of cardiovascular diseases, as it contributes to myocardial hypertrophy and indirectly to higher mortality of patients with CKD [17, 33].

The results of the present study should be analyzed considering some limitations. Despite being a population-based sample, the individuals allocated were limited to those treated in a reference health unit linked to the Family Health Strategy, which may affect the generalization of the results. Another limiting fact is based on the food issue. Although eating habits have an important impact on BP reduction, this study should have evaluated them, considering the logistical difficulty in applying dietary recalls. However, all participants were asked if the unit's professionals about adopting consistent eating habits to control hypertension instructed them. Another question infers the sample size; although it is sufficient for the analysis, there is a limitation of the cross-sectional design, making it impossible to establish causal relationships between exposure and disease development.

In conclusion, although hypertension has a multifactorial etiology, obesity, smoking, and glycemia were the risk factors positively correlated with it. Given this, it is essential to intensify the control of hypertension and cardiovascular risk factors, aiming to reduce or control morbidity and mortality through prevention and better quality of life for the population.

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Beliefs and Attitudes in Women with Gestational Diabetes Mellitus. A Systematic Review

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Abstract- *Introduction:* The purpose of this research is to review systematic review of the most significant studies on the belief system and attitudes of pregnant women diagnosed with Diabetes Mellitus Gestational (GDM) within the framework of the psychosocial dimensions of this condition.

Materials and methods: A systematic review based on the PRISMA methodology in PubMed/Medline, Scielo, Hindawi, Springer Link and BMC Medicine and inclusion and exclusion criteria were defined.

Results: 207 papers were found to whom the abstract was reviewed after duplicates were discarded, leaving 180 articles, to which the inclusion and exclusion criteria were applied, and 28 articles were selected at the end that provided relevant information for the objectives of the study. study. Results found allow us to infer the presence of a belief system around the consequences of gestational diabetes for pregnant women and their babies.

Keywords: *beliefs, attitudes, gestational diabetes mellitus, systematic review.*

GJMR-F Classification: *DDC Code: 616.462 LCC Code: RC660.4*

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Beliefs and Attitudes in Women with Gestational Diabetes Mellitus. A Systematic Review

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Conclusions: Psychosocial variables such as attitudes, beliefs, motivation, among others, exert an influence in relation to the appearance and management of gestational diabetes and should be considered in the formulation of interventions and prevention programs for this condition.

Keywords: beliefs, attitudes, gestational diabetes mellitus, systematic review.

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I. Introduction

Among the most common diseases that can occur gestational diabetes is found during pregnancy. Is characterized due to hyperglycemia with values that, despite being higher than normal, are lower than those established to diagnose diabetes. This type diabetes usually occurs after 20 weeks of gestation (World Health Organization, 2020; Palani et al., 2014).

The definition postulated by the International Classification of Diseases in his 10th edition categorizes this condition in the section "maternal diseases that can affect the fetus" with the code "O24 Diabetes Mellitus in pregnancy". And it is defined as "an alteration in the metabolism of carbohydrates, which is diagnosed for the first time during the state of pregnancy. It is a condition of insulin resistance, generally presents after the fifth month of gestation" (ICD-10, 2008, p.245).

It´s necessary take into account that in gestational diabetes symptoms occasionally are not evident. However, they could present some because of high blood sugar levels. These include that patients may be thirstier than usual more frequent and heavier urination or feeling very tired or fatigued (Martínez de Salinas 2017; Gracia & Olmedo, 2017).

Some other effects associated with impaired glucose recorded in various investigations are: visual disturbances, excessive hunger, headache, headache, stomach aches, disorientation, difficulty concentrating and lethargy (American Diabetes Association, 2002). It's essential that pregnant women undergo the pertinent examinations, which should be carried out around the fifth month of pregnancy a blood glucose test to identify the pathology in time (González Ruiz et al., 2014).

Researchers have been able to point out a large number of complications that arise in pregnant women diagnosed with GDM such as increased risks for fetal abnormalities including macrosomia, neonatal hypoglycemia, respiratory distress syndrome, alteration in the development of the islet cells and malformations in the development (Reyes Burgos & Guillén Matos 2015; Crowther et al., 2005).

Concomitant to this medical symptomatology, there are some factors that could have a psychological impact and affect the quality of life of women with gestational diabetes, which can even be more serious than the pathology itself. Some of them would be

associated with the severity and intensity of self-care tasks, the interference of these tasks in daily life, fear of complications and symptoms of hyperglycemia that can affect psychosocial and occupational functioning (Rubin, 2000; Craig, et al., 2020; Jones, Roche & Appel 2009).

Therefore, it is possible that, once the disease has been identified, the patients experience certain impediments in complying with the medical prescriptions, which are almost always associated with the lack of education and with skills in the management of the pathology.

According to what has been pointed out by various researchers, variables related to the complexity of the treatment (because it is clear that long periods of time to recover from this condition), together with the lack of visible immediate reinforcements, (because the effects of prevention will really be seen in the long term), can make the diagnosis of GDM and its condition a heavy burden for patients (Gatchel, Oordt & Oordt, 2003; Sacks 2014).

Several authors affirm that the lack of effective communication with the health professionals and the costs to be incurred by patients and their families to deal with the problem also hinder the success of medical interventions (Lakshmi et al., 2018).

It is important to mention that not all pregnant women have the same risk of GDM. The evidence shows that there are some factors that lead and can produce it, such as high levels of blood glucose, family history of diabetes, overweight before pregnancy or weight gain during this period, present syndrome of polycystic ovary, excessive amniotic fluid, unexplained miscarriage or stillbirth, high blood pressure, lead a sedentary lifestyle, be over 25 when you get pregnant, and having had a previous diagnosis of diabetes (ADA, 2011; Cartin, 2011).

Therefore, it is necessary to emphasize the importance of the psychoeducation of these women so that they can acquire habits and lifestyles. such as eating healthy foods, reducing fat, reduce sugar intake, avoid drug and alcohol use, exercise regularly, sufficient and adequate controls doctors, and even understand some references of the complications that can happen in pregnancy, including the presence of GDM.

It is opportune to have information that lets the woman know that she is condition is a public health problem of great relevance and that, if not If treated quickly, it can cause various alterations to the mother and the baby.

Delving into the psychological dimension that has been considered in paragraphs previous ones, it could be said that the literature and the evidence scientific report in relation to GDM. For example, various authors recorded the appearance of depressive symptoms during and after this type of diagnosis (Antos, Nowak, & Olszewski, 2013; Díaz, et al., 2013; Dame, et al., 2017).

But in the same way there is evidence related to the presence of anxiety, stress, low self-esteem, feelings of guilt, difficulties in feeding, insomnia (Tellería, 2014; Hinkle, et al., 2016). I also know have pointed out alterations or dysfunctionalities in the social plane such as isolation, decreased communication with friends and family, difficulties with the couple, decreased function and sexual appetite, among others.

As has been seen, a significant number of investigations have been carried out on this topic that can be framed within the psychosocial perspective of GDM. Particularly in the systematic review carried out by Devsam, Bogossian & Peacock, (2013), in which 19 studies were identified who met the inclusion criteria.

Three fundamental categories stand out in this work: a) reaction initial diagnosis, in which negative thoughts are observed, feelings of loss of control, identity changes and adaptation the changes; b) concern approach, in which there is evidence of concerns about the health of the baby and the perceived severity of the DMG. Finally, category c) influencing factors is recorded, which includes cultural roles and beliefs, social stigmas, social support, support professional, adequate and appropriate information, social roles and barriers for self-care.

In any case, the results of this systematic review highlight the importance of the psychosocial considerations presents in this type of patients, among which we can mention: the psychological impact of the diagnosis, the importance of overcoming anxiety and stress to achieve better adherence to treatment, the necessary adaptation in the patient's relationship with family and health personnel, need to reduce the negative charge, both cognitively and affective, that have people who have been diagnosed with GDM, among other.

Of all these psychosocial considerations, one in particular has generated the interest of this investigative group that are the beliefs and attitudes of women diagnosed with GDM. And that is, if it can be found a dimension that leads to generate some kind of model to help the women with GDM, it would be represented by the set of cognitions, attitudes and representations that at one moment a woman has to whom diagnosis was made during pregnancy.

Around this theme there are important approximations, such as the research developed by Chávez-Courtois, et al., (2013), in which it is observed how the cognitive structure of women with GDM presents symptoms such as confusion; despair and recurring ideas; records of thoughts of the type: “my son is going to come with malformations”, “I am going to die”, “my son is not going to come into the world”, “this pathology is irreversible”, “why did it happen to me”.

There is also evidence of a flow of beliefs in relationship with guilt and low self-esteem.

Despite how unflattering the previous results are, the knowledge of these beliefs, attitudes and social representations of women with GDM, can be an important input in the adequacy of guides and guidelines for the psychosocial accompaniment of women with this diagnosis, which incidentally, at least in the Latin American context, are quite scarce, reducing, in the cases in which they exist, to guides of a medical care type, ignoring the transcendent of both social and psychological variables, not only in the appearance of pathology, but in its management.

It is clear then that knowledge of beliefs, cognitions and attitudes of women with GDM, will allow progress in aspects as crucial as helping patients to adhere to treatment, generate psychoeducational models, understand the pathology and its treatment and even involve the family group and the couple in managing not only the pathology, but throughout the pregnancy process. For this reason, it is presented this research that has the purpose of carrying out a systematic review around the cognitions and beliefs present in women with gestational diabetes mellitus.

II. Materials and Methods

- Design and type of study: This is a systematic review carried out with the methodology of the Cochrane Collaboration (Higgins and Green, 2011) and the PRISMA statement and checklist (Moher, Liberati, Tetzlaff, and Altman, 2010).
- Search strategy: Inquiries were made in the databases of Pubmed, Scielo, Hindawi, Springer Link and BMC Medicine data, in order to identify scientific articles in English and Spanish from 2000 to 2021. The exploration was limited to the last two decades due to the interest that the scientific community has presented in the psychosocial factors associated with the GDM (Jiménez-Chafey and Dávila, 2007). Also made supplementary manual searches and retrieved the articles that met the inclusion criteria. Descriptors were used using booleans that included DMG and beliefs, attitudes and cognitions.
- Inclusion Criteria: Studies with female participants over 18 years of age (assured in one way or another by the presence of a consolidated belief system) diagnosed with GDM. Studies on the belief system, cognitions, attitudes, frames of reference and social representations. In addition, observational studies were included.
- Exclusion Criteria: Studies with samples of women under 18 years old. Likewise, studies belonging to gray literature, studies reviewed in blogs or web pages of public or private institutions.
- Selection of studies: It is presented in the PRISMA flowchart described in Figure 1. Of the 85 preselected articles, it was read the full text to arrive at a final selection that included 28 articles.
- Data extraction and analysis: A matrix was constructed that included the consulted database, article title, author, keywords, methodology, results, conclusions. Additionally, a review was constructed for each of the research included in this review. These are the supplies principles for the analysis of the results and the conclusions of this study.

III. Results

Of the 28 articles selected to be included in this systematic review (Figure 1), the most important results are indicated below.

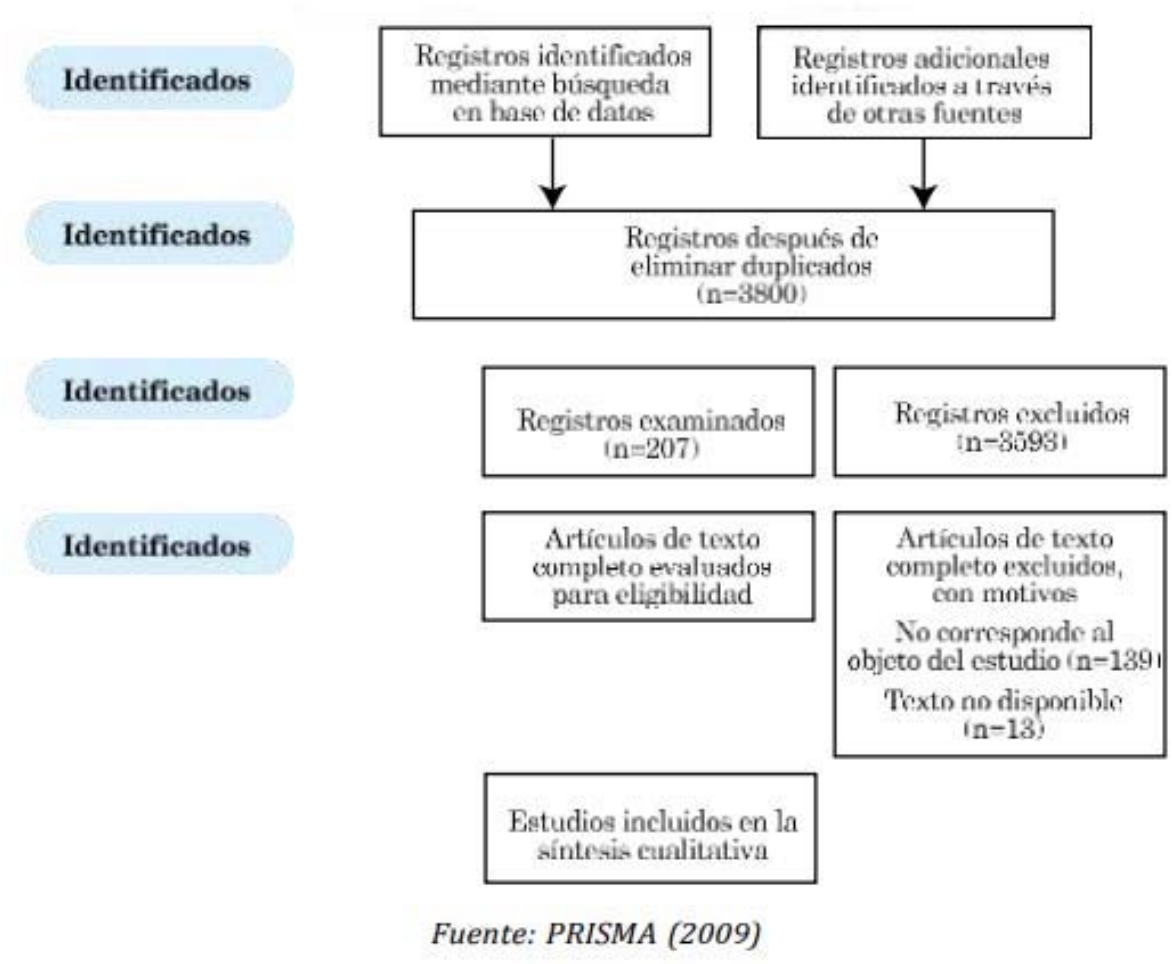

Figura 1: Diagrama de flujo PRISMA 2009

A first element in the beliefs of women with GDM is related to with what happens after diagnosis. On a recurring basis the Patients state that they experience a stress condition in which a significant number of cognitions associated with impairment arise of the future health, not only of them, but of the unborn babies.

They experience GDM as a burden and a threat to the baby-mother dyad (Razee et al., 2010; Tellería 2014; Dalfrà et al., 2011). On the other hand, many of the women may have the belief that GDM will lead to in chronic diabetes that they will suffer from for the rest of their lives. It is important to highlight that many of the beliefs, including the fears that may arise derive from the information provided by the hospital institution and health personnel (Hjelm et al., 2008; Hjelm et al., 2018).

The investigative group of Dalfrà and collaborators (2011), also investigated in their works some psychosocial variables such as depression and certain cognitions. These studies were conducted in both women with GDM, such as in patients with type II diabetes. It was possible to establish that These patients generally present depressive symptoms, which are closely related to a perception of poor health.

The issue for women is complicated if they have other children who are younger than they depend on them. Some have support from their extended family, but others they must leave their children with people who are not their family. Only with the purpose of offering a reference is the testimony of a woman diagnosed with GDM: “I was suddenly hospitalized with diabetes and I couldn't get some belongings home before I was hospitalized” (Araujo et al., 2013).

On the other hand, Chávez-Courtois et al., (2014) who approached the system of beliefs, perception and experiences of women with DMG, report valuable findings. Several of the women with this condition are very certain that, although it is a delicate pathology, the self-care practices, physical exercise, diet and, in general, medical recommendations, will augur good results in overcoming the diabetes. The women interviewed for this research generally they are quite clear about the risks and lifestyles that are not healthy that can lead to the generation of GDM.

Among the most significant answers that can be considered are: "I feel that the disease has to do with eating food with a lot of sugar, or eating late. Also, I

hardly ever ate breakfast. I have generally had bad eating habits". In other cases, there are thoughts of these women, around the fact that it is a hereditary condition. And in several cases patients feel guilty for not having healthy habits before and during pregnancy.

In fact, in the study by Hjelm et al., (2018), the influence of these psychosocial variables. African migrant women residing in Sweden were compared with women from the European country where both groups were diagnosed with GDM. It was found that women from Africa did not know what GDM was and its causes and how consequently they had a passive attitude of self-care. Coincidentally you are patients reported more pregnancy-related problems. In contrast, Swedish women had higher risk awareness, higher concern for your health and that of your baby and therefore more self-care, including the use of medications.

The importance of culture is also evidenced in the research carried out in an Asian context by Ge, et al., (2016), in which It seems that a diagnosis of GDM does not cause major concerns, as it could be in western countries. Some of the women with these types of diagnoses just let nature take its course and they rely a lot on the type of food they consume. Thoughts regarding this condition are not as negative and generally believe will have a good prognosis, which makes the emotional and family effect don't be so dramatic.

In the meta-analysis by Chida & Hamer (2008), in which they wanted to establish the incidence of adverse psychosocial factors with poor control of diabetes, statistically significant associations were found. This was determined through pooled correlation coefficients $r = 0.096$, $p = 0.006$). In the same sense, the lack of social support also contributes to poor control of diabetes.

In the study carried out by Ansarzadeh et al., (2020), in which negative correlations between quality of life and the presence of GDM that reach -0.78, a positive correlation was found between the results obtained by the participants in the scale of knowledge, attitudes and self-care and the results obtained in social support.

Patients with GDM who have the perception that they have with high levels of social support and a high level of knowledge of the pathology, tend to have positive attitudes towards their condition and generally high levels of self-care. On the other hand, the research shows that the presence of levels of anguish is correlated negatively with self-management. That is, before levels of anguish, little can the person do to contribute from their own management to leave forward in the pathology suffered. In this case the correlation is reported in -0.857. There is also a positive correlation between the level of knowledge and self-management, equivalent to 0.848.

On the other hand, Park et al.,(2018), start from the assumption that breastfeeding affects positively in the metabolic regulation of women with GDM, also favoring that these pregnant patients decrease the probability of developing type II diabetes after pregnancy (Kelishadi & Farajyan, 2014; Brahm & Valdés, 2017).

As has been recorded through these results, from various perspectives that articulate the research and theoretical interests of health and disease with the social sciences, we wanted to find the incidence of psychosocial variables such as attitude, motivation, personality, beliefs, among others, in the health of patients and/or in the effectiveness of medical procedures (Limonero and Bayés, 1995; Arranz et al., 2003; Mancuso et al., 2006; Pineapple Booksellers, 2012; Oblitas Guadalupe et al., 2017). Which is actually not an easy task.

For example, in the research by Hussain et al., (2015), an attempt was made to explore the relationship between the attitude of patients, satisfaction with treatment and the decrease in glycemic levels in patients with GDM, which would give rise to thinking about overcoming the pathology in these women. Although there were no conclusive results, this study was able to demonstrate that the presence of negative attitudes and levels Low satisfaction with treatment correlates with high glycemic levels.

There are other investigations that, although they were not developed exactly with women with GDM, are somewhat related to variables associated with the appearance of this pathology.

In the work of Lindsay et al., (2019), carried out with pregnant women for the first time developing excessive body weight, it was established that These women do not know exactly what the line is between being overweight and the obesity. That is, most of the study participants did not they knew if their body weight was in the healthy range. In addition, most of the women had accepting attitudes towards their weight gain, which suggests that pregnant women have beliefs related to the fact that weight gain is normal among pregnant.

On the other hand, there is also research interested in trying to modify psychosocial dimensions (habits, beliefs, lifestyles) in women diagnosed with GDM (Represas Carrera, 2021; Jelsma et al., 2016).Generally, these studies are carried out through interventions controlled. Brown et al., (2017), conducted lifestyle interventions with GDM in about 4501 women.

Intervention programs included physical activity, diet, blood glucose self-monitoring, health education. Results show some very important data such as the fact that women belonging to the experimental groups have a lower probability of develop postpartum depression. Additionally, these women improve their body weight significantly. From this investigative perspective there is quite hopeful findings for psychosocial treatment, both of women with GDM, as in diabetic patients of all kinds.

Finally, systematic reviews were consulted, such as the one developed by Craig et al., (2020), in relation to attitudes, perceptions and experiences of the women with GDM. These authors in a rigorous search and after ruling out several studies, they identified some 840 articles dealing with the theme in question.

After applying the inclusion and exclusion criteria, they reviewed full text 88 documents. Carrying out a systematization of these articles, 8 key themes of the experiences and subjectivities of women with GDM were identified: initial psychosocial impact, communication of the diagnosis, perception of irrigation, management before the DMG, load of the diagnosis of GDM, social support and gaining control.

IV. Discussion

The aim of this review was to conduct a systematic review around cognitions and beliefs present in women with GDM to improve knowledge of the pathology and adherence to treatment, generate models psychoeducational and involve the family group and the couple in the management only of the pathology, but throughout the pregnancy process.

In this research it was possible to establish that the beliefs and cognitions of women with this condition are located in two great edges. One of them called living experiences that bring happiness and the second experiencing experiences that cause suffering (Araujo et al., 2013).

Accordingly, it can be inferred that pregnant mothers with GDM, alternately run between these two polarities. surely there is some patients in whom one experience prevails more than the other. The most recurrent cognitions related to happiness are related to with ideas like “I am going to be a mother; I am with other women in the same conditions as mine and we will have a treatment that will help us overcome the pathology".

While the negative thoughts are located in the fact of moving away from home and in the pathology itself and its consequences, leading them to generate fear of their own death or that of their babies. Some recalled deaths of family members and acquaintances from illnesses associated with diabetes.

Going a little deeper into this negative set of cognitions and thoughts related to the diagnosis of GDM, it is necessary to mention the appearance of feelings of sadness, unfailingly articulated with human cognition system.

If the diagnosis is received untimely, as usually happens, recurrent thoughts full of concern associated with a number of events such as abrupt removal from home, hospitalization, loss of the continuity of daily life and the abrupt rupture of relationships relatives.

Other studies report the existence of beliefs around three themes fundamental: illness, health and self-care, which are formed as expected, due to the effects of socialization, education and previous experiences. Furthermore, the evidence shows that this system of beliefs remains stable over time (Hjelm et al., 2018).

However, a situation that worries women recurrently is the real possibility of having to make changes in their lifestyles, especially everything on topics such as diet or exercise. They are also concerned about the possibility having to take insulin.

In the field of health and disease, beliefs report a central element, both in health promotion and prevention of the disease, fundamental axes that cannot be left aside. In fact, care programs must be nourished by dimensions derived from culture, from the characteristics of groups, from the idiosyncrasies of peoples, from values, attitudes and beliefs and from other number of psychosocial variables. These elements are taken up by authors to adapt models around social education in health, called Health Belief Models (Rosenstock et al., 1988).

Accordingly, the beliefs and in general the cognitive system of the women with GDM depend largely on cultural dimensions and on the way in which societies construct their social representation of disease in general and particular pathologies.

The study of cognitions in people with GDM is important not only because such aspects are necessary in program design aimed at improving adherence to treatment and reducing food harmful for this type of patients.

There is something even more complex, and it is the fact that, although research is still incipient, this type of psychosocial variables (conditions cognitive difficulties, behavioral coping and the use of social support) presented in a negative way, can lead to stress and the appearance of various pathologies (Chida & Hamer 2008; Luceño Moreno et al., 2004; Vieco Gómez & Abello Llanos, 2014; Fernandez-Prada et al., 2017).

Ideas and cognitions that women with GDM have related to that this type of pathology can lead to a chronic disease such as type I or II diabetes, which some may think is irrational, Tellería (2014) highlights it as a belief that would act as a protective factor for initiate self-care behaviors in relation to eating and physical activity. This same author emphasizes that invariably the Women with this diagnosis tend to develop depression, anxiety, changes in their thoughts and attitudes about their lifestyles. The Anxiety is often related to future health.

Under this consideration, it is very important then, that the system of beliefs of these people allows the existence of favorable attitudes towards breastfeeding and also towards activities that promote health, to have higher levels of self-efficacy, greater perceived benefit, and less alcohol consumption.

But in reality the most relevant in relation to life experiences of women with this diagnosis and their cognitions, is that in general patients focus their thoughts, behaviors and motivation, around changes in their lifestyles to overcome the pathology and to prevent future problems for them and their babies, not only during the gestation period but also after childbirth.

V. Conclusions

From this systematic review, firstly, it was observed that immediately after diagnosis women are invaded by a series of ruminations and thoughts that denote the level of concern in your belief system. Among the most recurrent ideas find "considering that this pathology will be irreversible, from now on Later I will have a chronic affectation, I will have to use insulin for life" and others. There are also ideas related to the fact that the pregnancy will not come to term and even that her life is in danger and of your baby.

Likewise, many consider that the pathology they are suffering from is due to the fact that they did not take the necessary care in relation to the diet before pregnancy and are generally blamed for the lifestyle adopted until that moment. Despite this, it is also recorded by many women with GDM, who in general terms do meet the medical prescriptions and adopt the recommendations of officials health to get ahead.

From what is observed, the belief system of doctors and nurse's health personnel in general, notably influences the attitudes and thoughts of these patients. Hence the recommendations and instructions of this personnel are so important to mark habits and practices that lead to the permanent search for the well-being of these patients. In this sense, a very important power of reference is observed on the part of the medical staff.

Another element found is that the emergence of beliefs and systems of thought in relation to health and disease originate from of the influence of parents, teachers, communication systems, processes of socialization, among others, which is why social and cultural variables are so telling in the formation of a certain system of beliefs. In addition, research shows that these systems are consolidated, being sometimes difficult to modify.

Although the investigation is still incipient, there are records that allow establish that psychosocial variables such as attitude, beliefs, cognitions, motivation, among others exert an influence on related to the appearance of certain pathologies. Similarly, variables of this type, like attitudes, beliefs, cognitions they can be quite promising for the management of many pathologies.

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Type 2 Diabetes Mellitus Remission in Patients with Ideal BMI in Rivers State, Nigeria

By Sokiprim Akoko, Iyeopu M. Siminialayi & Sunday Chineye

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Abstract- *Background:* When Type 2 Diabetes patients are in resource-restrained environments with little access to sustainable care, weight increase is linked to poor glycemic control from insulin resistance. Safer, locally accessible, and scientifically supported methods of managing their health become a priority when they lack effective access to medical treatment and medicines as a result of poverty. Targeted lifestyle therapies have been shown to be clinically beneficial and reasonably priced for the prevention and management of diabetes today. This research seeks to assess the effectiveness of a purely Nigerian diet in helping people with type 2 diabetes mellitus lose weight and maintain excellent glycaemic control.

Method: Randomization was used to divide the sixty research participants into treatment (dietary caloric restriction intervention) and control (standard of care) groups that were matched. Samples were gathered for analysis at baseline, midline, and at the conclusion of the trial throughout the participants' 24-week follow-up period.

Keywords: *type 2 diabetes, diet, intervention, hba1c, glycaemic control, remission, waist circumference and BMI.*

GJMR-F Classification: *NLMC Code: WK 810*

Strictly as per the compliance and regulations of:

Type 2 Diabetes Mellitus Remission in Patients with Ideal BMI in Rivers State, Nigeria

Sokiprim Akoko [α], Iyeopu M. Siminialayi [σ] & Sunday Chineye [ρ]

Abstract- Background: When Type 2 Diabetes patients are in resource-restrained environments with little access to sustainable care, weight increase is linked to poor glycemic control from insulin resistance. Safer, locally accessible, and scientifically supported methods of managing their health become a priority when they lack effective access to medical treatment and medicines as a result of poverty. Targeted lifestyle therapies have been shown to be clinically beneficial and reasonably priced for the prevention and management of diabetes today. This research seeks to assess the effectiveness of a purely Nigerian diet in helping people with type 2 diabetes mellitus lose weight and maintain excellent glycaemic control.

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Result: In contrast to the outcome from the intervention group, which showed a considerable weight reduction after six months, the BMI in the standard of care group experienced a gradual decline in mean values (from 26.06 to 25.0), which was not statistically significant. Mean waist size reduced from 88.82 cm to 80.0 cm (p=0.001), and BMI dropped from 26.76 kg/m2 to 22.77 kg/m (p=0.001). After six months, the patients' HbA1c decreased from the initial visit, where the mean was 7.617, to mean =6.017. Within the intervention group, the mean fasting blood sugar decreased from a group mean of 7.97 on the initial visit to a mean of 5.35 after six months. Furthermore, this study demonstrated that just three of the 17 patients with perfect BMI in the standard of care group had a decrease in HbA1c of 6.5 or less, but in the intervention group, 61% of patients with ideal BMI had HbA1c of 6.5%. The difference that was noticed was statistically significant (p=0.025), nevertheless. Thus, following 6 months of management without the use of oral hypoglycemic medications, there is a strong correlation between a decrease in BMI and a decrease in HbA1c to a normal level in individuals with T2DM.

Conclusion: In keeping with the definition of remission, fourteen of the 23 participant who has normal BMI maintained normal HBA1c for 6 months. Normalizing BMI with caloric restriction is an effective means of controlling blood glucose and type 2 diabetes mellitus.

Keywords: type 2 diabetes, diet, intervention, hba1c, glycaemic control, remission, waist circumference and BMI.

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I. Introduction

When Type 2 Diabetes patients are in resource-restrained environments with little access to sustainable care, weight increase is linked to poor glycemic control from insulin resistance. Safer, locally accessible, and scientifically supported methods of managing their health become a priority when they lack effective access to medical treatment and medicines as a result of poverty and non-medication adherence. (Sokiprim et al, 2022). Targeted lifestyle therapies have been shown to be clinically beneficial and reasonably priced for the prevention and management of diabetes today.

The rise in T2DM over the past 50 years is strongly tied to lifestyle modifications. The number of those with T2DM has risen as our lives have changed to incorporate more processed meals and less physical activity (John et al., 2018). Non-communicable illnesses are becoming a worldwide scourge, affecting both those in and above poverty. Since Nigeria has the greatest prevalence and burden of diabetes in Sub-Saharan Africa, everyone in Nigeria must prioritize getting treatment (Chinenye et al., 2014). It is impossible to overstate the importance of natural antioxidants and nutrients in avoiding illness.

Diabetes caused just under 2 million deaths yearly, ranking as the sixth most common cause of death in the world in 2016. Africa will have a 109% increase in T2DM from 2013 to 2025, closely followed by the Middle East and North Africa with 96%. The estimated worldwide rise is 55%. (John et al., 2018). 33% of male children and 39% of female children born after 2000 will acquire T2DM. (2014) Wilmot and Idris Additionally, having T2DM makes you more likely to get Alzheimer's as you age. (Barbaallo and Dominguez, 2014).

Although diet and exercise are the first steps to successfully avoid and even manage diabetes without the use of medications, the main objective of dietary usage in treating T2DM is to lower risk factors and avert complications brought on by the condition. The idea that dietary and lifestyle choices might considerably help drive type 2 diabetes into remission is currently receiving mainstream support (John, 2018).

Since the majority of the proposed dietary therapies for T2DM are Western in origin and difficult for the average Nigerian to get or observe, it may be difficult to modify them for usage locally. In order to design a

menu for T2DM individuals that complies with normal operating standards, this study aims to employ regional, easily accessible whole plant-based choices.

Diet however, is a known modifier of and regulator of NFkB through phytonutrient and antioxidant formation, causing a down regulation of NFkB production and gene modulation that occurs from NFkB pathway. This down regulation has not been fully achieved with medications in management of non communicable diseases.

Finally, while many individuals may have access to food, they could not have the money to pay for medical treatment. For these people with T2DM, using meals they are currently accustomed to promote health and wellness would be very beneficial. These research on dietary adjustment (exclusively Nigerian foods) in T2DM haven't received much attention, yet the results will aid T2DM patients' health outcomes.

T2DM medications are not without dangers and negative effects (Siminialayi et al., 2006). When glycaemic management was improved for 3-5 years with pharmaceuticals, ADVANCE Collaborative Group (2008) and Ling et al. (2009) found that this did not lessen macrovascular consequences because of epigenetic alterations.

This research seeks to assess the effectiveness of a purely Nigerian diet in helping people with type 2 diabetes mellitus lose weight and maintain excellent glycaemic control in the University of Port Harcourt Teaching Hospital, Rivers State, Nigeria.

II. Materials and Methods

a) Research Approach

Ethical approval was sought and obtained from the Ethics Review Committee of the University of Port Harcourt (Annex 1) with reference number UPH/CEREMAD/REC/MM71/001.

Sixty study participants were randomly assigned and matched evenly into the two groups (Standard of Care-Control and Dietary Intervention-Treatment). These individuals were randomized into matched control (standard of care) and treatment (dietary calorie restriction intervention) groups. They were known diabetics who attended a diabetes clinic and were followed up for 24 full weeks (August 2021 to February 2022). Throughout the trial, the control group and the intervention group both reported their FBS on a biweekly basis.

ANOVA was used to conduct a test of significance for each of the two sets of observations (within the control and intervention group). Then, to completely exclude the impact of variables on the treatment group, a more robust statistic with better experimental sensitivity, such as ANCOVA, was used to guarantee that significance in the treatment group is attributable to intervention (Kpolovie, 2010).

Microsoft Office Excel 2017 was used for the graphics, and Statistical Packages for Social Science (SPSS) version 22.0 was used for the statistical analysis. For the analysis of the data, the study used the following statistics: descriptive statistics for cleaning the data, stem-and-leaf plots and box plots for spotting and eliminating outliers, Kolmogorov-Smirnov tests, and histograms for determining normality. The research issues and study hypotheses were addressed using crosstab and frequency, ANOVA and ANCOVA, and significant variables were submitted to post hoc or pairwise comparison tests (i.e. Bonferroni test). The Mann-Whitney U test was used for independent samples (such as anthropometric characteristics) and the Wilcoxon signed-rank test was used for dependent samples (such as FBS) to examine the statistical significance of the differences between means. The cutoff point for statistical significance between means was chosen at 0.05. Using Pearson's linear correlation, the associations between the indices were assessed, with the level of statistical significance set at p 0.05 at 95% confidence.

b) Recruitments

Participants were chosen from among the diabetes patients who visited the University of Port Harcourt, Nigeria's General Outpatient and Diabetes Clinics. Patients had to be known diabetics, 18 years of age or older, not be using any herbal, conventional, or complementary medications in the two weeks before to the study's start, and not be taking any drugs that are known to affect pancreatic or kidney function. Additionally, patients with poorly controlled blood sugar at the most recent routine clinical check, BMIs of >26 kg/m2 and 45 kg/m2, patients with pre-existing co-morbidities or complications of diabetes, patients who were critically ill, and patients who were taking drugs that affected the mind were disqualified.

Each participant gave their agreement before the study's 60 participants were randomly assigned to the open label control (Standard of care) or intervention arms. The intervention group got a calorie-restricted meal made up of items that were cultivated nearby, whereas the control arm included diabetes patients who were taking at least one oral hypoglycemic medication. To make sure there was no statistically significant difference between the control and intervention groups, statistical tests were conducted.

All trial participants underwent clinical evaluations and assessments of adherence and morbidity once per month. At least once a week, all participants were phoned on their cell phones to check in and address any issues that came up as the research went along. Participants whose clinical symptoms worsened were taken out of the trial and started receiving complete pharmacological therapy under the care of an endocrinologist until their circumstances

stabilized. Every participant underwent a self-reported fasting blood glucose test every two weeks. The study's endpoints were an FBS value that remained between 3.5 and 5.5 mmol/l for six months and a weight loss of 5% of body weight.

III. Results and Discussion

a) Demographics

Demographic characteristics showed no statistically significant difference between Age (p=0.934), Gender (p=0.605), and the clinical group, as shown in Table 1.

Table 1: Demographics

Variable	Group		χ^2 (p-value)
	Intervention n_2=30	Control n_2=30	
	Freq (%)	Freq (%)	
Age Group			
30-49	11 (36.67)	9 (30.0)	
50-69	15 (50.0)	17 (56.67)	0.934$^{\alpha}$
≥70	4 (13.33)	4 (13.33)	
Mean (SD)	54.73 ± 11.29	57.6 ± 9.73	1.05 (0.292)$^{\mu}$
Gender			
Male	13 (43.33)	16 (53.33)	
Female	17 (56.67)	14 (46.67)	0.27 (0.605)

**Statistically significant (p<0.05); χ^2=Chi-Square; μ=Student t-test; α=Fishers Exact p*

b) Association between clinical parameters for Standard of Care (Control) group over 6 months

Results from Table 2 shows mean differences in the clinical parameters (FBS, waist circumference and BMI) of T2DM patients subjected to a standard of care (Control) over a 6months period. Changes in means were noted in FBS, and waist circumference parameters in the standard of care group but for BMI that had steady drop in mean values (from 26.06 to 25.0). ANOVA results of the clinical parameters on the average presented show no significant mean differences for all the measured clinical parameters after a period of six months. As such the null hypothesis of no significant mean difference is sustained. Therefore, there are no significant mean differences on the clinical parameters (FBS, waist circumference and BMI) of T2DM patients subjected to a standard of care (Control) over a 6months period.

Table 2: Descriptive Statistics showing an association between clinical parameters for the Standard of Care (Control) group

Variables	Standard of Care (Control) group		ANOVA (F-test)	p-value
	Mean	SD		
FBS CONTROL				
Initial	8.570	3.3124		
3 Months	7.003	2.3839	2.298	0.107
6 Months	7.367	3.1119		
Overall	7.647	3.0059		
Waist CONTROL				
Initial	90.817	10.9359		
3 Months	89.800	10.6298	0.078	0.925
6 Months	90.000	10.1608		
Overall	90.206	10.4701		
BMI CONTROL				
Initial	26.907	4.5521		
3 Months	26.093	4.5572	0.763	0.469
6 Months	25.417	4.9173		
Overall	26.139	4.6662		

NS-Not Significant at P > 0.01; ANOVA=Analysis of variance

c) *Association between clinical parameters for Intervention group over a 6 months Period*

Results from Table 3 shows mean differences on the clinical parameters (FBS, waist circumference and BMI) of T2DM patients subjected to Intervention over a 6months period.

The One-way analysis of variance was conducted to investigate if there are significant mean differences on the clinical parameters (FBS, waist circumference and BMI) of T2DM patients subjected to Intervention over a 6months period. ANOVA results, presented in the above table, show significant mean differences for all the clinical parameters. There are significant mean differences on the clinical parameters (FBS, waist circumference and BMI) of T2DM patients subjected to Intervention therapy over a 6months period. Thus, the intervention had no significant effect on the Lipid profile of T2DM patients after six months.

Table 3: Statistical descriptions of the association between clinical parameters in Intervention group

Variables	Intervention group		ANOVA (F-test)	p-value
	Mean	SD		
FBS CONTROL				
Initial	3.8471	0.7024		
3 Months	1.9670	0.3591	7.388	**0.001***
6 Months	1.5855	0.2895		
Overall	2.8416	0.2995		
Waist CONTROL				
Initial	88.82	9.900		
3 Months	82.93	8.777	7.572	**0.001***
6 Months	80.00	8.034		
Overall	83.92	9.574		
BMI CONTROL				
Initial	26.670	4.1194		
3 Months	24.920	4.0177	7.667	**0.001***
6 Months	22.857	3.1076		
Overall	24.816	4.0487		

**Statistically Significant at P ≤ 0.05; ANOVA=Analysis of variance*

d) *Percentage of Fasting Blood Sugar (FBS) Reduction at the Individual Level after six months of Standard of Care (Control) and Intervention*

Results from Table 4 show that after a period of six months, the intervention controlled the FBS level of 30% of T2DM patients, and the standard of care controlled the FBS level of 13% of T2DM patients. Therefore, the intervention has the efficacy to control the FBS in more than twice the number of T2DM patients as the standard of care. However, this observed difference was not statistically significant (p=0.237).

Table 4: Percentage of Reduction of FBS using both Standard of Care (Control) and Intervention after a period of six months

Group	All participants n (%)	FBS Change n (%)			% Reduction (*No. of normal subjects after 6months – Initial no. of normal)*	Fishers exact p
		Initial	3 Months	6 Months		
Control	30 (100.0)	8/30 (26.7)	12/30 (40.0)	12/30 (40.0)	12-8 4 (13.33)	
Intervention	30 (100.0)	11/30 (36.67)	13/30 (43.33)	20/30 (66.67)	20-11 9 (30.0)	0.237$^{\mu}$

μ=Fisher's exact p (recommended where cell values are <5)

Table 5: Percentage of Normal Body Mass Index (BMI) that had reduction in HbA1c to <6.5% within the Standard of Care (Control) and Intervention groups after a period of six months

Group	All participants n (%)	BMI Change n (%)			Fishers exact p
		Initial	3 Months	6 Months	
Control	30 (100.0)				
Ideal (BMI)		12/30 (40.0)	15/30 (50.0)	17/30 (56.7)	
(HbA1c <6.5%)Remission		0 (0)	3/15 (20.0)	3/17 (17.6)	**0.025$^{\mu*}$**
Intervention	30 (100.0)				
Ideal BMI		11/30 (36.7)	16/30 (53.3)	23/30 (76.7)	
(HbA1c<6.5%)Remission		2/11 (18.18)	9/16 (56.25)	14/23 (60.87)	

**Statistically Significant at P ≤ 0.05; μ=Fisher's exact p (recommended where cell values are <5)*

e) Assessing the effect of Individual on the FBS level of T2DM patients while controlling for the influence of standard of care

The analysis of covariance was conducted to investigate the effect of Intervention group on the fasting blood sugar (FBS) level of T2DM patients over a period of six months while controlling for the influence of standard of care. ANCOVA results, presented in Table 6 show a significant difference in mean FBS level amongst treatment groups [$F(2, 86) = 6.790$, $p < .01$, partial $\eta 2 = .136$]. However, the calculated effect size indicates a small proportion of variance accounted for about 13.6% change in the FBS level of the treatment group.

Table 6: ANCOVA Summary of the effect of Intervention on FBS level of T2DM patients

Parameter	Effect of Intervention on the FBS level			F	P-value	Effect Size η^2
	Initial Visit	3 Months	6 Months			
	Mean ± SD	Mean ± SD	Mean ± SD			
FBS Intervention	7.94 ± 1.97	6.42 ± 1.95	5.36 ± 1.94	6.790	**0.002***	0.136

**Statistically Significant at P ≤ 0.05*

f) Assessing the effect of Intervention on the BMI level of T2DM patients while controlling for the influence of standard of care

The analysis of covariance was conducted to investigate the effect of MNT therapy on the Body Mass Index (BMI) of T2DM patients over a period of six months while controlling for the influence of standard of care. ANCOVA results, presented in Table 7, show a significant difference in mean FBS level amongst treatment groups [$F(2, 86) = 8.333$, $p < .01$, partial $\eta 2 = .162$]. However, the calculated effect size indicates a small proportion of variance which accounted for about 16.2% change in the BMI of the treatment group.

Table 7: ANCOVA Summary of the effect of Intervention on BMI of T2DM patients

Parameter	Effect of Intervention on the BMI Control			F	P-value	Effect Size η^2
	Initial Visit	3 Months	6 Months			
	Mean ± SD	Mean ± SD	Mean ± SD			
BMI Intervention Group	26.76 ± 2.74	24.92 ± 2.73	22.77 ± 2.74	8.333	**0.001***	0.162

**Statistically Significant at P ≤ 0.05*

g) Assessing the effect of Intervention on the Waist circumference of T2DM patients while controlling for the influence of standard of care

The analysis of covariance was conducted to investigate the effect of Intervention on the waist circumference of T2DM patients over a period of six months while controlling for the influence of standard of care. ANCOVA results, presented in Table 8, show a significant difference in mean waist circumference (weight loss) amongst treatment groups [$F(2, 86) = 7.435$, $p < .01$, partial eta $\eta 2 = .147$]. However, the calculated effect size indicates a small proportion of variance, accounting for about 14.7% change in the waist circumference of patients in the treatment group.

Table 8: ANCOVA Summary of the effect of Intervention on Waist circumference of T2DM patients

Parameter	Effect of Intervention on the Waist Circumference			F	P-value	Effect Size η^2
	Initial Visit	3 Months	6 Months			
	Mean ± SD	Mean ± SD	Mean ± SD			
Waist Circumference	88.75 ± 6.47	82.98 ± 5.73	80.02 ± 6.74	7.435	**0 .001***	0.147

**Statistically Significant at P ≤ 0.05*

IV. Discussion

Even with a large number of T2DM medications being available on the market, non-adherence to therapy, side effects, cost, and poor health seeking behaviors are a major drawback for effective glycaemic control. (Jaja et al., 2016; Sokiprim et al., 2022; Siminialayi and Eme-Chioma, 2006) This occasionally makes it difficult for patients with T2DM to follow through to their treatment. An unhealthy diet like non-vegetarian with processed red meat, excess fats were even reported to have a 3.8times chance of having diabetes linked to their cause of death irrespective of age and sex. (Snowden 1985). Although this study considered age, sex and dietary patterns, it did not the health seeking behaviours and occupations of the participant. It showed a mean age of 54.74±11.29 years for intervention group with gender equally matched (see Table1).

The principles of prevention and management in T2DM include frequent blood glucose monitoring, reduction in calories etc. Blood glucose monitoring before and after meal will enable early recognition of glucose abnormalities and allow prompt action to prevent several diabetic complications. Particpants in this study had blood sugar monitored daily on self-assessment of daily glycaemic control. Tonstadetal. (2013) showed that appropriate diet was associated with weight reduction in patients at risk for T2DM when BMI was adjusted. The intervention group were on 1,200kcal per day in this present study. A UK study demonstrates that a weight loss program can result in type 2 diabetes remission even in those with a normal body mass index (BMI) by reducing body fat, notably in the liver and pancreas. Twenty participants with type 2 diabetes with a BMI of 27 kg/m2 or less participated in the ReTUNE (Reversal of Type 2 Diabetes Upon Normalisation of Energy Intake in Non-obese People) experiment. Participants had shed 9% of their body weight after a year. They observed reductions in liver fat, total triglycerides, and pancreatic fat, and their body fat considerably dropped, reaching the same level as individuals without type 2 diabetes. This was also shown to be associated by increases in insulin production and decreases in A1c and fasting plasma glucose levels, Furthermore, the study showed that T2DM has the same etiology and pathogenesis whether BMI is normal or elevated. This knowledge ought to have a significant impact on the recommendations doctors give to their patients. Encourage patients to lose weight is not very pleasant to a patient with T2DM however, this is one of the dramatic aspects about dealing with people in this group. The improvements in T2DM are seen with systematic intervention programs that result in considerable weight reduction (Katula et al., 2013; Mohammed et al., 2012). For the prevention and treatment of diabetes, targeted lifestyle interventions have been demonstrated to be both clinically and financially successful (Shurney 2012; Herman, 2015). The study showed a steady drop of parameter means from the initial visit to six months in the intervention group. The fasting blood sugar dropped from a group mean of 7.97 on the initial visit to a mean of 5.35 after six months with and effect size of 0.13. (see Table 6). Furthermore, the study showed that twice the number of study participants in the intervention group had a drop in Fasting blood glucose (well controlled) throughout the study period compared to the control group in a ratio of almost 2:1. It is safe to document that the intervention had more efficacy at glycaemic control (see Table 4). Lim et al 2011 found normalized in the diabetic group (from 9.2±0.4mmol/L to 5.9±0.4 mmol/l, p=0.003). This finding were similar to finding in Pories et al. (1987), affirmed in 2017 by Schauer et al.; reaffirmed by the Diabetes Remission Clinical Trial (DiRECT) study and currently by Sokiprim et al (2022) using wholly Nigerian diet to achieve remission in T2DM patients. Similarly, the result showed substantive weight loss after six months of Intervention. This is revealed in the waist circumference mean which fell from 88.82cm to 80.0cm after six months, and BMI that dropped from 26.670 to 22.857kg/m^2 after six months (Table 3). The very small effect size of 0.16 for BMI shows no interference with the control (Table 7).

This study has provided proof that a healthy diet may help maintain good glycaemic control and restore patients' health to normal. A calorie reduction over a period of weeks or months may cause weight loss with a decline in leptin synthesis, a reduction in fatty acid infiltration into liver and muscle cells, and the potential for a legacy effect. This may be the cause of the outcome seen with the decrease in HbA1c after weight loss (see table 5). All of them cause weight reduction, a decrease in inflammatory mediators, and an increase in insulin sensitivity. Dysbiosis is brought on by the disturbance of the microbiome caused by the Western

diet, antibiotics, and other factors, as well as a decrease in the synthesis of the short-chain fatty acid butyrate, which helps control blood sugar. Studies shows that a high fibre-based diet helped to reverse diabetes despite no weight loss occurring implying the type of food consumed impacted blood sugar regulation. (Trapp et al. 2010; Oputa and Chineye, 2015).

The study's observations of changes occurred quickly. The participant receiving one call and two texts each week as follow-up for rewards and long-term health education might be the cause of this. They were reminded to take daily blood sugar readings, keep a chart, and follow the research protocol during the calls, which served as the psychological support and interactions they needed to deal with worries during the study time (Akoko et al, 2022). Additionally, it assisted in keeping an eye on potential problems both inside and across groups. If long-term lifestyle interventions are not supported, sustainable improvements may be phased out due to a lack of an adequate support structure and unfavorable environmental factors, such as no immediate financial advantage to the hospital where the study was conducted. According to Van Ommen et al. (2017), the theory and practice are different, and we are facing a multifaceted dilemma that calls for removing obstacles on the basis of the economy, society, psychology, and biology.

The study provides some evidence that weight loss can improve glycaemic control and insulin sensitivity, returning to normal blood sugar levels in patients with T2DM and caloric restrictions to 1,200 kcal per day. As a result, doctors are encouraged to emphasize the need for selfcare in these patients once again. The limited sample size and persistence of the glycaemic control after achieving blood sugar control for six months are the study's shortcomings. When standard of care variables were taken into consideration, the study demonstrated the viability of diet in weight loss and glycemic management (control group). Evidence may be seen in the analysis of covariance for the FBS (Tables 6), BMI (Tables 7) and waist circumference (Tables 8). It is advised to conduct more research to determine the longevity of the Nigerian diet's ability to maintain remission and ameliorate organ effects of poorly controlled T2DM

V. Conclusion

In keeping with the definition of remission, fourteen of the 23 participant who has normal BMI maintained normal HBA1c for 6 months. Normalizing BMI with caloric restriction is an effective means of controlling blood glucose and type 2 diabetes mellitus.

The Authors of this study declares *no conflict of interest.*

The authors also acknowledge the limitations with the study as some results were self-reported by study Participants.

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Preferred Author Guidelines

We accept the manuscript submissions in any standard (generic) format.

We typeset manuscripts using advanced typesetting tools like Adobe In Design, CorelDraw, TeXnicCenter, and TeXStudio. We usually recommend authors submit their research using any standard format they are comfortable with, and let Global Journals do the rest.

Alternatively, you can download our basic template from https://globaljournals.org/Template

Authors should submit their complete paper/article, including text illustrations, graphics, conclusions, artwork, and tables. Authors who are not able to submit manuscript using the form above can email the manuscript department at submit@globaljournals.org or get in touch with chiefeditor@globaljournals.org if they wish to send the abstract before submission.

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Authors must ensure the information provided during the submission of a paper is authentic. Please go through the following checklist before submitting:

1. Authors must go through the complete author guideline and understand and *agree to Global Journals' ethics and code of conduct,* along with author responsibilities.
2. Authors must accept the privacy policy, terms, and conditions of Global Journals.
3. Ensure corresponding author's email address and postal address are accurate and reachable.
4. Manuscript to be submitted must include keywords, an abstract, a paper title, co-author(s') names and details (email address, name, phone number, and institution), figures and illustrations in vector format including appropriate captions, tables, including titles and footnotes, a conclusion, results, acknowledgments and references.
5. Authors should submit paper in a ZIP archive if any supplementary files are required along with the paper.
6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

Declaration of Conflicts of Interest

It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

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- Writings
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- Printed material
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2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

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The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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