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Association of CYP17 and MTRR Gene

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Association of *CYP17* and *MTRR* Gene Polymorphisms with Clinicopathological Features of Breast Cancer Patients

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Abstract- Allele frequencies of T-34C *CYP17* and A66G *MTRR* polymorphisms in breast cancer samples and the correlation with clinicopathological data can contribute to the prognosis and knowledge of the genetic profile of a population. In this study, was analized the association of T-34C *CYP17* and A66G *MTRR* polymorphisms with clinicopathological data in 82 samples of invasive ductal breast carcinoma in the Southwest region of Bahia. PCR-RFLP was used to determine the genotypes for A66G *MTRR* and T-34C *CYP17* polymorphisms. The allele frequency was 0.369 and 0.631 for A66G *MTRR*; 0.672 and 0.328 for T-34C *CYP17*. The A66G *MTRR* genotypes showed deviation from Hardy–Weinberg equilibrium ($p=0.000$), the genotypes are not segregating independently ($p=0.036$). No association of polymorphisms with clinicopathological features was observed.

Keywords: *Breast cancer, CYP17, MTRR, polymorphism.*

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Association of *CYP17* and *MTRR* Gene Polymorphisms with Clinicopathological Features of Breast Cancer Patients

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I. Introduction

According to the International Agency for Research on Cancer (IARC, 2019), breast cancer is the most prevalent neoplasm among women worldwide, with invasive ductal carcinoma (IDC) of the breast being the most common histological type, corresponding to about 80%. Like all cancers, breast cancer is a multifactorial disease with environmental and genetic factors as causes (Rojas & Stuckey, 2016).

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It is used several clinical and pathological factors to define the prognosis of the disease as well as to determine the most appropriate therapy. These factors include demographic (age, preand postmenopausal status and ethnicity) and the tumor characteristics (affected axillary lymph nodes, tumor size, type and histological grade, expression of hormone receptors, and HER2) (Schnitt, 2010). Also, studies of genetic polymorphisms associated with breast cancer has contributed to the understanding of the biology of this disease as well as to the discovery of new genetic susceptibility markers that may assist in the prognosis and therapeutic management of the disease (Lilyquist, Ruddy, Vachon & Couch, 2018; Low, Zembutsu, & Nakamura, 2018).

Polymorphisms of the *CYP17* and *MTRR* genes have been the target of studies since they are related to pathways for breast carcinogenesis: estrogen biosynthesis and methionine biosynthesis (Mo, Ding, Zheng, Zou & Ding, 2020; Sun et al., 2018). *MTRR* gene codes for the enzyme methionine synthase reductase which is responsible for the active state of the enzyme MTR (methionine synthase), which catalyzes the addition of a methyl group to homocysteine thus forming methionine. SAM (S-adenosylmethionine) receives the methyl group of methionine, the universal donor molecule of the methyl group responsible for the methylation profile of DNA (Bottiglieri, 2005; Hiraoka & Kagawa, 2017; Weiner et al., 2012). Studies of the A66G polymorphism of the *MTRR* gene indicate that the G allele decreases the activity of the MTRR enzyme, thus being able to influence homocysteine levels (Olteanu, Munson & Banerjee, 2002). Therefore, disturbances in this metabolic pathway are associated with the carcinogenesis process as they interfere in the pathways responsible for maintaining the pattern of DNA methylation of the cell (Hasan et al., 2019).

The *CYP17* gene codes for a cytochrome P450 enzyme. This enzyme participates in two stages of estrogen biosynthesis from cholesterol (Guo et al., 2006). One of the polymorphisms of the *CYP17* gene is the T-34C located in the 5´ UTR (5´untraslated region) of the promoter. This mutation potentiates promoter

activity by increasing *CYP17* expression (Carey et al., 1994) and estrogen levels (Clemons & Goss, 2001), which is associated with an increased risk of breast cancer (Wen, Wu, Fu, Wang, & Zhou, 2017).

The frequency of polymorphic alleles observed in the population can show an ethnographic variation (Binia et al., 2014). The Brazilian, and especially the population of the state of Bahia, is known to be highly admixture because of the initial composition formed by Amerindians, European, and African descendants (Abé-Sandes, Silva Junior & Zago, 2004). The knowledge of the frequencies of the polymorphic alleles of *CYP17* and *MTRR* in the samples of invasive ductal breast carcinoma and the correlation of these alleles with clinical and pathological characteristics can contribute to the knowledge of the prognostic and genetic profile of women the Northeast of Brazil

Thus, this study analyzed the combined association of T-34C *CYP17* and A66G *MTRR* polymorphisms with clinical and pathological aspects (age, tumor size, histological grade, and lymph node involvement) in patients with invasive ductal breast carcinoma in the Southwest region of Bahia.

II. Methods

a) Subjects

Approval was obtained by the Research Ethics Committee of the State University of Southwest Bahia (UESB) Vitoria da Conquista, Brazil. The population of interest was composed of 82 unrelated subjects with histopathological diagnosis of invasive ductal breast carcinoma.

b) Genotype determination

The DNA was extracted from tumoral breast tissue embedded in a paraffin block using the QIAamp DNA FFPE Tissue (https://www.qiagen.com/us/). Polymerase Chain Reaction followed by Restriction Fragment Length Polymorphism (PCR-RFLP) was used to determine genotypes for the two polymorphic regions A66G *MTRR* and T-34C CYP17 using the primer strings: (F) 5'GCAAAGGCCATCGCAGAAGACAT3' and (R) 5'GTGAAGATCTGCAGAAAATCCATGTA3' (Wilson et al., 1999) and (F) 5′CAAGGTGAAGATCAGGGTAG3′ and (R) 5′GCTAGGGTAAGCAGCAAGAG3′ (Kuligina et al., 2000), respectively. Was performed a PCR according to the following protocol: 2,5 μM reaction buffer 10x (Invitrogen), 2,5 mM $MgCl_2$ (Invitrogen), 1,25 mM dNTPs (Invitrogen), 2,5 mM of each primer (Invitrogen), 1U of Taq DNA polymerase (Invitrogen). Sample were exposed to 94°C for 5 min (initiation), 35 cycles at 94°C for 30s (denaturation), 60°C (A66G *MTRR*) or 57°C (T-34C *CYP17*) for 40s (annealing) and 72°C for 30s (extension). The reaction was finalized with the extension at 72°C for 5 minutes. The check of the PCR products was on a 3% agarose gel stained with ethidium bromide and visualized an L-PIX HE transilluminator (Locus Biotechnology). For A66G MTRR and T-34C CYP17 were observed fragments of 66 bp (base pairs) and 145 bp, respectively.

The digest of the PCR product A66G *MTRR* (66 bp) was performed by the *NdeI* restriction enzyme (Thermo Scientific) at 37°C for 1 hour (Wilson et al., 1999). The substitution A>G eliminates the restriction site for the *NedI* enzyme. Therefore, after digestion, wild homozygotes (AA) generate fragments of 44 bp and 22 bp, and mutant homozygotes (GG) were not digested, remaining at 66 bp. Heterozygotes (AG) have fragments of 66, 44, and 22 bp after digestion. The digestion product was checked on 10% polyacrylamide gel and subsequently visualized after staining with silver nitrate.

The digest of the PCR product of polymorphism T-34C *CYP17* (145 bp) was used the *MspA1* restriction enzyme (Thermo Scientific) at 37°C for 4 hours (Kuligina et al., 2000). The substitution T>C generate a restriction site for the *MspA1* enzyme. Were generated fragments of 145 bp; 75 and 70 bp; and 45, 75 and 70 bp after digestion for wild homozygous (TT), mutant homozygous (CC), and mutant heterozygous (TC), respectively. The check of the digest products was on a 5% agarose gel stained with ethidium bromide.

c) Statistical Analysis

Analyses of the Hardy–Weinberg equilibrium and Linkage disequilibrium for unconnected loci were made for each polymorphism, both using Genepop (4.2 version). The $\chi 2$ tests were used for analyses of differences in genotype frequency. The association between the genetic polymorphisms A66G *MTRR* and T-34C *CYP17* and clinical-pathological features were determined by odds ratio (OR) and corresponding 95% confidence intervals (95% CIs). We compared A66G *MTRR* and T-34C *CYP17* alleles and genotype distributions in subgroups of subjects (age: >49 and <49; histological grade: I+II and III+IV; tumor size: <3 and >3; lymph node involvement: yes and no).

III. Results

Were included eighty-two women in this study. Clinical-pathological features were available *(Table 1)*. Fifteen (18.3%) subjects are under 49 years of age at the time of diagnosis. Most have histological grade II (42.7%) and tumor size >3 cm (71.9%). Lymph node involvement was present in (54.9%) of subjects (Table 1).

Table 1: Clinical-pathological features of the 82 unrelated breast cancer subjects

Clinical-pathological features	Number (%)
Age (years)	
30-49	15 (18.3%)
50-69	32 (39%)
70-99	32(39%)
Unknown	3 (3.7%)
Histological grade	
I	15 (18.3%)
II	35 (42.7%)
III	17 (20.7%)
IV	1 (1.2%)
Unknown	14 (17%)
Tumor size (cm)	
<3	23 (28.1%)
>3	59 (71.9%)
Lymph node involvement	
Yes	45 (54.9%)
No	23 (28.1%)
Unknown	14 (17.1%)

The allele frequency was 0.369 and 0.631 for A66G *MTRR* polymorphism; 0.672 and 0.328 for T-34C *CYP17* polymorphism. The distribution of genotypes of T-34C *CYP17* polymorphism showed no deviation from Hardy–Weinberg equilibrium ($p=0.278$). However, A66G *MTRR* polymorphism not aligned to Hardy–Weinberg equilibrium ($p=0.000$), were found at higher and low frequency for the AG and AA genotypes, respectively *(Table 2)*. Analyses of genotypic linkage disequilibrium showed that the genotypes were not segregating independently ($p=0.036$). No allele or genotype for A66G *MTRR* and T-34C *CYP17* were associated with the clinical-pathological features of subjects *(Table 3)*.

Table 2: Allele and genotype frequencies of polymorphic regions A66G *MTRR* and T-34C *CYP17* in 82 unrelated breast cancer subjects.

Genotype or allele	Frequency (%)	*χ2*	*p-value*
A66G MTRR			
A	0.369		
G	0.631		
AA	2.5	8.10	**0.01**
AG	68,8	8.75	**0.01**
GG	28,7	2.53	0.2
T-34C CYP17			
T	0.672		
C	0.328		
TT	41.8	0.13	0.95
TC	50.7	0.53	0.70
CC	7.5	0.57	0.70

Abbreviations: χ2: chi-square. Statistically significant: p=0.05.

Table 3: Odds ratio of clinical-pathological features between polymorphic regions A66G MTRR and T-34C CYP17 in 82 unrelated breast cancer subjects.

Genotypes or alleles	Clinical-pathological features							
	Age (>49 and <49)		Histological grade (I+II and III+IV)		Tumor size (<3 and >3)		Lymph node involvement (yes and no)	
A66G MTRR	**OR (CI 95%)**	***p-value***	**OR (CI 95%)**	***p-value***	**OR (CI 95%)**	***p-value***	**OR (CI 95%)**	***p-value***
A	1.00 (Reference)	-	1.00 (Reference)	-	1.00(Reference)	-	1.00(Reference)	-
G	1.12 (0.52-2.43)	0.76	0.93 (0.45-1.94)	0.85	0.91 (0.49-1.75)	0.79	0.99 (0.50-1.93)	0.97
AA	1.00 (Reference))	-	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
AG	0.95 (0.39-2.26)	0.90	1.02 (0.44-2.35)	0.96	0.96 (0.45-2.05)	0.91	1.02 (0.46-2.27)	0.96
GG	1.45 (0.38-5.58)	0.59	0.82 (0.23-2.85)	0.75	0.86 (0.31-2.39)	0.78	0.94 (0.33-2.70)	0.92
T-34C CYP17								
T	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
C	0.75 (0.30-1.86)	0.53	0.46 (0.14-1.56)	0.21	0.91 (0.40-2.07)	0.82	1.45 (0.55-3.84)	0.45
TT	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-	1.00 (Reference)	-
TC	1.00 (0.35-2.89)	0.99	0.67 (0.19-2.23)	0.49	0.61 (0.26-1.44)	0.26	1.40 (0.48-4.11)	0.54
CC	0.36 (0.05-2.36)	0.29	0.45 (0.02-9.26)	0.60	4.75 (0.2589.89)	0.29	1.60 (0.16-15.44)	0.68

Abbreviations: odds ratio (OR); confidence intervals (CI).Statistically significant: p=0.05

IV. Discussion

Over the past few years, studies on the association between the A66G *MTRR* and T-34C *CYP17* polymorphisms with breast cancer have been controversial, which has confirmed in the meta-analyses carried out for both the A66G *MTRR* polymorphism (Hu, Zhou, Wang, & Wang, 2010; Mo et al., 2020; Wang, Li, Wang, He, & Xi, 2017) and for the T-34C *CYP17* (Chen & Pei, 2010; Sun et al., 2018) with a greater tendency towards the absence of association. In this sense, should be considering that the frequency of the analyzed alleles can vary according to the population studied (Binia et al., 2014; Kato, Cichon, Yee, Land, & Korczak, 2009) and that the cancer is a multifactorial disease. Not only genetic factors (genes with high, low and moderate penetrance)(Apostolou & Fostira, 2013; Shiovitz & Korde, 2015) but also environmental factors contribute together to the risk of developing breast cancer (Apostolou & Fostira, 2013; Stratton & Rahman, 2008; Syamala et al., 2010).

In this study, conducted with 82 women with breast IDC in the southwestern region of Bahia, the analyzes performed did not indicate an association between the A66G *MTRR,* T-34C *CYP17* polymorphisms with clinical-pathological aspects such as age, tumor size, and histological grade. The analyzes showed an excess of heterozygotes for the *MTRR* locus, indicating a deviation from the Hardy-Weinberg principle. Additionally, the genotypes are not segregating independently. These findings may be due the probable admixture of the studied population, as well as the effect of the distribution of genotypic frequencies in samples of women with breast IDC not being random.

In a population in Canada was not found an association between the *CYP17* polymorphism and the increased risk for breast cancer and the degree of the tumor. However, their results suggest that the gene polymorphisms that control the formation and availability of estrogen interact significantly with other risk factors such as estrogen receptor (ER) status, use of oral contraceptives and pre-menopause, influencing an increased risk for this neoplasm (Cribb et al.,2011). In a study conducted with Chinese women, it was found that the presence of the TC genotype significantly increased the risk of postmenopausal breast cancer (Zhang et al., 2009). Also, other evidence indicated a possible impact on menopausal status, age at menarche, and BMI (Body Mass Index) in the association between the *CYP17* T-34C polymorphism and the risk of breast cancer, as verified by a meta-analysis (Chen & Pei, 2010).

Regarding the *MTRR* polymorphism, although studies indicate that this polymorphism does not confer an increased risk for breast cancer (Hu et al., 2010; Weiner et al., 2012), work carried by Suzuki et al., (2008) pointed that polymorphisms *MTRR* and *MTHFR* were associated with individual susceptibility to breast cancer in post-menopausal women. The reported studies, therefore, demonstrate a probable association of these polymorphisms with other clinical factors not evaluated by us, such as menopausal status, age at menarche, and BMI, aspects that are not available for our analyzes.

Studies of the association of genetic polymorphisms with clinical and pathological aspects in different neoplasms seek to contribute to the knowledge of the prognostic profile of patients and thus collaborate not only in the diagnosis and establishment of the best treatment but also in the prevention of the disease. However, the frequencies of alleles can differ depending on the population studied, and it is important that these types of studies are carried out in different populations to establish the genetic profile of each region.

The limitation of this study is the low number of samples and the absence of controls. Thus, the expansion of the sample number, as well as the analysis of the frequencies of these polymorphisms in control samples, may provide a better understanding of the effect of these polymorphisms on breast cancer in our population.

V. Conclusions

Altogether, the data did not indicate an association between the A66G of *MTRR* and T-34C of *CYP17* polymorphisms with some clinicopathological features of invasive ductal breast carcinoma. Although these findings need further validation, our data contribute to the analysis of the genetic profile of women with breast cancer in the Northeast of Brazil and understanding diverse aspects of breast cancer biology.

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Pregnancy during the Sars-Cov-19 Pandemic

By Gulchekhra Agzamovna Jalilova, Nilufar Farhadovna Rasulova
& Nigora Saydmukhtarovna Mukhamedova

Abstract- Here we present a COVID-19 review during pregnancy, combining various factors necessary for understanding pathophysiology and susceptibility, diagnostic problems with time-domain analysis of reverse transcriptional chain reaction (RT-PCR), therapeutic inconsistencies, intrauterine response, and maternal-fetal, complications. We discuss the latest options for antiviral therapy and vaccine development, including the new use of chloroquine in the body of COVID-19. Fetal supervision, given the predisposition to growth restriction and special considerations in childbirth, is being addressed. In addition, we have provided basic services. Our clinical care model is built on the principles of segregation in the workplace, responsible social sharing, localization of cross-infection among healthcare providers, the wise use of personal protective equipment and telemedicine. Our goal is to ensure the appropriate safety of patients and healthcare providers based on it.

Keywords: *pandemic, COVID-19, pregnancy, gynecology, mothercare.*

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Pregnancy during the Sars-Cov-19 Pandemic

Gulchekhra Agzamovna Jalilova [α], Nilufar Farhadovna Rasulova [σ]
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Abstract- **Here we present a COVID-19 review during pregnancy, combining various factors necessary for understanding pathophysiology and susceptibility, diagnostic problems with time-domain analysis of reverse transcriptional chain reaction (RT-PCR), therapeutic inconsistencies, intrauterine response, and maternal-fetal, complications. We discuss the latest options for antiviral therapy and vaccine development, including the new use of chloroquine in the body of COVID-19. Fetal supervision, given the predisposition to growth restriction and special considerations in childbirth, is being addressed. In addition, we have provided basic services. Our clinical care model is built on the principles of segregation in the workplace, responsible social sharing, localization of cross-infection among healthcare providers, the wise use of personal protective equipment and telemedicine. Our goal is to ensure the appropriate safety of patients and healthcare providers based on it.**

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I. Introduction

A pregnant woman and her fetus are at high risk during outbreaks of infectious diseases. To date, the literature has published the outcomes of 55 pregnant women infected with COVID-19, and about 46 newborns, while there is no accurate evidence of vertical transmission of the infection [1, 2].

Physiological changes and mechanical factors during pregnancy increase susceptibility to infections in general, especially with the involvement of the cardio-respiratory system, which contributes to the rapid development of respiratory failure in pregnant women [3, 4, 5]. In addition, the shift during pregnancy to the dominance of the type 2 T-helper system (Th2) protecting the fetus makes the mother vulnerable to viral infections that are more effectively controlled by the type 1 T-helper system (Th1). These unique challenges require an integrated approach to pregnant women exposed to SARS-CoV-2. We present a COVID-19 review during pregnancy, combining various factors necessary to understand pathophysiology and susceptibility, diagnostic difficulties with a real-time reverse transcription polymerase chain reaction test (rOT-PCR), therapeutic inconsistencies, intrauterine transmission, and maternal complications and fetus [6].

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We are considering the latest types of antiviral therapy and vaccine development, including the use of chloroquine in the treatment of COVID-19. The issues of fetal monitoring in the light of the predisposition to intrauterine growth retardation and the special points regarding childbirth and delivery are considered. In addition, we emphasize the safety of obstetric medical personnel who are at the forefront, while continuing to provide the necessary treatment. Our clinical support model is based on the principles of separation in the workplace, responsible social exclusion, containment of cross-infection among medical workers, the wise use of personal protective equipment and telemedicine. Our goal is to share a system that can be adopted by tertiary obstetric institutions that lead pregnant women in a pandemic, but the safety of patients and health workers is paramount.

The most important component in the fight against any threat of infectious diseases is the treatment of vulnerable groups. It is known that pregnant women suffer disproportionately from respiratory diseases, which are associated with increased infectious morbidity and high maternal mortality rates. Although most human coronavirus infections are mild, epidemics of the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) epidemics over the past two decades have been especially serious, where approximately a third of pregnant pregnant women have died from the disease [7, 8, 9, 10]. The current outbreak of pneumonia from coronavirus infection in 2019 (COVID-19) caused by coronavirus type 2 of severe acute respiratory syndrome SARS-CoV-2, was declared a pandemic by the World Health Organization (WHO) on March 11, 2020, the peak of which is predicted to occur in April 2020, without significantly reducing the ability to transmit the virus. Due to the universal and steady spread of the disease across all continents, we are likely to see women with COVID-19 in all trimesters of pregnancy. In this article, we summarize the clinical features of pregnant women with COVID-19 and want to introduce a practical and integrated system that focuses on the obstetric difficulties of managing this disease during pregnancy.

a) Pregnancy Complications

So far, maternal COVID-19 outcomes are more promising than SARS and MERS. The combined data show that mortality was 0%, 18% and 25% for COVID-19, SARS and MERS, respectively - in the last two diseases, the most common causes were progressive

respiratory failure and severe sepsis 27, 28. This is not surprising, given the predisposition to bacterial superinfection due to direct mucosal damage, dysregulation of immune responses and changes in the microbiome of the respiratory tract after viral pneumonia29. Postnatal maternal deterioration may still occur, requiring continuous monitoring. Complications of COVID-19 for the fetus include miscarriage (2%), intrauterine growth retardation (CDW; 10%) and premature birth (39%) [11, 12, 13]. Fever with an average temperature of 38.1-39 ° C is the predominant symptom with COVID-19; cohort studies in patients with other infections did not show an increased risk of congenital abnormalities from maternal hyperthermia in the first trimester, although attention disorders are more common in these children, which may be associated with hyperthermic damage to the fetal neurons [14].

b) Vertical transmission

There is a theoretical risk of vertical transmission similar to that observed with SARS, since the ACE2 receptor is widely expressed in the placenta with a similar receptor-binding domain structure between SARS-CoV-1 and SARS-CoV-2. More recently, it was reported that two newborns in mothers infected with COVID-19 gave a positive result on SARS-CoV-2 shortly after birth, which raises concerns about the possibility of vertical transmission. However, there were no confirmed cases of vertical transmission among 46 other newborns, born to COVID-19 infected mothers, which have been reported to date, which is confirmed, in turn, by evidence indicating the absence of virus isolation from amniotic fluid, umbilical cord blood, breast milk, and throat swabs taken from this patient sample. It is noteworthy, however, that the vast majority of these women contracted COVID-19 in the third trimester - there is currently no data on perinatal outcomes in cases where the infection was infected in the early stages of pregnancy. Regardless of the risk, it is encouraging that in children, COVID-19 appears as a mild respiratory illness [16, 17, 18].

c) Childbirth, delivery and breastfeeding

Women arriving at the maternity ward are divided according to local rules into low, medium and high risk of COVID-19 identification to determine where the patient will be referred and the precautions required by the nursing staff.

The type of delivery is determined by obstetric and clinical urgency factors. Since there is no convincing evidence of vertical transmission of the virus, vaginal delivery is not contraindicated in patients with COVID-19 [19, 20]. When urgent delivery is required in women in critical condition, Cesarean section is the most appropriate: indications include a sharp deterioration in the state of the woman in labor, difficulties with mechanical ventilation due to the pregnant uterus, and inhibition of the fetus. Delivery, including cesarean section, should be performed using a full set of personal protective equipment and in a room with negative pressure. A widespread method of pain relief during childbirth is the patient's self-adjustable nitrous oxide and oxygen delivery.

However, contamination of gas supply equipment with respiratory viruses may be a hidden source of cross-contamination and medical personnel should be familiar with the general rules for disinfecting equipment, including the treatment of an outlet valve (valve) between patients, and the use of a microbiological filter (with pore size <0.05 μm) between mouthpiece or face mask. In the same way, women with suspected or confirmed COVID-19 and who require oxygen during childbirth should wear a surgical mask over the nasal cannula, since moistening of the kylorol will aerosolize (or spray) the infected droplets within a radius of about 0.4 meters, where the result may there is a risk of nosocomial drip infection [21, 22].

Although the available data do not confirm the risk of vertical transmission, according to the recommendations of the Canadian Society of Obstetricians and Gynecologists for SARS in pregnant women, after childbirth, you should refrain from delayed clamping of the umbilical cord, as well as from contact between the skin of the mother and newborn. Based on current published guidelines, breastfeeding is not contraindicated.

A retrospective analysis of COVID-19 during pregnancy showed that none of the women contained traces of SARS-CoV-2 virus in breast milk. Nevertheless, if the patient decides to breastfeed, then in view of the proximity between the mother and the child, she should wear a protective mask to prevent the transmission of the virus to the child by drip [23, 24, 25]. The presence of antibodies to coronavirus in breast milk depends on the gestational age at which the mother was infected, and whether high doses of corticosteroids have been used that can suppress the mother's immune response.

II. Conclusion

Pregnant women are a uniquely vulnerable group in any outbreak of an infectious disease due to their altered physiology, sensitivity to infections, and impaired mechanical factors and immune function. The need to protect the fetus adds additional difficulties in maintaining their health. Special precautions are needed to reduce the possibility of cross-contamination of medical personnel during medical procedures that require close physical contact and predispose to drip infection, such as vaginal delivery. Most obstetric care is based on consensus recommendations and best practice recommendations, while evidence is emerging on the clinical effectiveness of antiviral therapy and the use of corticosteroids. This review is a comprehensive system to ensure the appropriate level of care for these

patients and for hospital staff during the COVID-19 pandemic.

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Resolving Late Consequences of Prenatal Stress with Dynamic Tandem Hypnotherapy (DTH)

By József P. Vas & Noémi Császár-Nagy

Abstract- Dynamic Tandem Hypnotherapy (DTH) was evolved more than ten years ago by the authors. It designates a kind of group-hypnotherapy, which is used for resolving late pathological consequences of prenatal traumas. In tandem hypnotherapy sessions more than two persons take part in: the patient and the co-therapist, who touch each other and go into a trance together; while the hypnotherapist keeps the distance. A mutual attunement is developed between the participants being in a tandem trance, which seems as serving for the therapeutic effect. Touch is considered as having the possibility to create calm, safety, and love, which are viewed to be lost or confined by unbearable emotions of prenatal traumas. Moreover, touch is viewed as the mother of perceptions, the "skin-ego," which already functions when there is no central nervous system developed yet. Thus consequences of prenatal stress can be healed with such a therapeutic approach at the same functional level on which the trauma occurred. Four case vignettes will be shown with interpretations upon how DTH works.

Keywords: *dynamic tandem hypnotherapy, prenatal stress, fetal consciousness, healing effects of DTH.*

GJMR-F Classification: *NLMC Code: QV 85, WM 415*

Strictly as per the compliance and regulations of:

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Abstract- **Dynamic Tandem Hypnotherapy (DTH) was evolved more than ten years ago by the authors. It designates a kind of group-hypnotherapy, which is used for resolving late pathological consequences of prenatal traumas. In tandem hypnotherapy sessions more than two persons take part in: the patient and the co-therapist, who touch each other and go into a trance together; while the hypnotherapist keeps the distance. A mutual attunement is developed between the participants being in a tandem trance, which seems as serving for the therapeutic effect. Touch is considered as having the possibility to create calm, safety, and love, which are viewed to be lost or confined by unbearable emotions of prenatal traumas. Moreover, touch is viewed as the mother of perceptions, the "skin-ego," which already functions when there is no central nervous system developed yet. Thus consequences of prenatal stress can be healed with such a therapeutic approach at the same functional level on which the trauma occurred. Four case vignettes will be shown with interpretations upon how DTH works.**

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I. Introduction

In 2009 we, the two authors, were working with a supervision group consisted of hypnotherapists, when, by accident, someone's prenatal trauma become resolved by an unusual setting in a way that the trauma-patient was hugged by a co-therapist (Noémi Császár-Nagy) while the hypnosis was managed by József Pál Vas. It was a discovery of a new hypnotherapeutic, more correctly, a recent psychotherapeutic method: a proximate one, which set had become relegated to the background of therapies since Freud had refused hypnosis. Then we used Dynamic Tandem Hypnotherapy more than 150 patients, whose individual psychotherapies had an impasse because we realized a cathartic and a catalyst effect of this method (Vas & Császár-Nagy, 2019). Actually, after an impasse resolved individual psychotherapy can be continued. The therapeutic effect seems as a joint attunement evolving between participants being in tandem trance.

Prenatal stress (Huizink, 2000) is viewed to lead to dysregulation of psychobiological functions caused by traumas of an expecting mother and her fetus in the form of either of the following: intrauterine infection (e.g. flu), the mother's severe somatic illness, intoxications, physical exhaustion and surgical intervention (Bergh, 2002; Chamberlain, 1993), Blighted Twin Syndrome (Robertson, 2010), the mother's negative emotional attitude toward or neglect of the baby. In addition important factors are death of family members (Austremann & Austermann, 2008), attempted artificial abortion and prenatal medical interventions, etc. (Champagne, 2008; Emerson, 1996; Hugo, 2009; Janus, 1997; Piontelli, 2010; Seelig, 1998; Seguí, 1995; Share, 1996; Veldman, 1999; Verny, 1996).

The epigenetic condition for the building up of a fetus' organism is the presence of the mother, who unfolds the fetus' genetic program. By this means, every pathological impact suffered either the fetus or the mother, a disturbed pathological development will take place in the mother–fetus bonding in the intrauterine phase (Carr, 1993). Prenatal pathological influences can all be considered as relational traumas, for prenatal stress always occurs within the context of the mother–fetus bonding (Blum, 1993; Raffai, 2002). Relational trauma leading to some flaw in the meeting of needs in the evolving fetus will act as an injury hindering the biopsychological maturation of the nervous system and the personality, with the archaic cerebral regions, such as the brainstem and the hypothalamus affected most.

According to the data of human developmental neurobiology the earlier the trauma occurs, the more archaic the cerebral region that might be involved in the resulting structural/functional disturbance leading to illness (Schore, 2003; Siegel, 1999). As a result of the damage, regulatory processes between the evolving corticolimbic regions will be disturbed (Schore, ibid. p. 33). The upset regulation may bring about enduring overstimulation and under stimulation and insufficient stress coping leading to severe psycho- and somatopathology. This disturbance of coping processes are viewed as implicit somatic memory, which will be repeated at the level of functioning against new forms of stress, which can lead to somatic, psychosomatic and psychological dysregulations and in the worst cases, disorders (Ferenczi, 1933, 1988).

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Interpersonal neurobiology views a mutual relationship between social interactions and gene expression. By virtue of this conception social interactions exert a direct effect on gene expression. This effect in turn modifies synaptic strength influencing the way social experiences affect your brain (Rossi, 2002). The psychotherapy of illnesses rooted in the prenatal periods must target the same developmental level on which the trauma occurred. Over the past decade's body-psychotherapies have been developed, which place their focus on the body (Balint M, 2001; Bálint K, 2005; Hertenstein,Holmes & McCullough, 2009; Meyer, 2010; Monzillo & Gronowicz, 2011; Phelan, 2009; Young, 2007; Zur & Nordmarkan, 2011). DHT developed by the authors in recent years is one of the techniques belonging to this group (Vas & Császár, 2011a, 2011b; Vas & Császár, 2013a, 2013b).

II. Method

By tandem, we mean an acronym for Touching Ancient & New Descendants Experiencing Mutuality (TANDEM). DHT involves the participation of more than two persons: the client, the co-therapist, and the hypnotherapist. During DHT, the co-therapist and the client go into a trance while touching each other. However, the hypnotherapist keeps the distance. DHT aims to elicit a positive, corrective experience with the potential of resolving the client's trauma. Touch is considered as having the possibility to create calm, safety, and love, which are viewed to be lost or confined by unbearable emotions of prenatal traumas (Heller, 1997; Hermann, 1934/1984). Thus, the essence of DHT seems to be a joint attunement evolving between participants being in a tandem trance. The attunement is viewed to have a therapeutic effect due to creating calm, acceptance, and love, which is shared in patient and co-therapist.

Some forms of DHT are used as

1. natural mother/father–child tandem hypnotherapy;
2. virtual mother/father–child tandem hypnotherapy;
3. virtual twin-type tandem hypnotherapy;
4. real twin-type tandem hypnotherapy;
5. patient–therapist dyad tandem hypnotherapy;
6. family tandem hypnotherapy with either real or virtual members of a family;
7. group tandem hypnotherapy with 5-10 participants.

This time more than 150 cases are under clinical investigation, which are viewed as suitable to study how the DHT works. All of the participants we will introduce in case vignettes were members of a psychotherapy group in which the therapist was Dr. Vas, and the co-therapist was Dr. Császár.

III. Results

Case vignettes

1. DTH with Virtual Mother and Son

One of the members of the group named Bill, is a 52 years old teacher, an anxious and perfectionist man, who has never been satisfied with himself. His statement about himself figures a specific character feature: "I start to do everything but never come to an end. I feel a continuous lag about it." As his mother told him he hadn't turned in time and was born from postponed labor. He knew that his father had wanted him as a girl. His father had never developed a close relationship with him.

He wanted to experience DTH to relive his prenatal period with a successful coping of destructive authority relating to his gender identity. From among the group members, he chose a woman to be his "mother" in tandem hypnosis, who exerted an impact on him with her tenderness. During tandem trance, he imagines to be a fetus in her mother's uterus and feels well. He wants neither to move at all. An original context occurs again since the therapist takes the role of his father, who didn't want him to be born as a boy. Thus his reluctance being born imaginatively in this hypnotherapy session is interpreted as resistance against his father's wish. Then the therapist takes his head with two hands and turns to initiate his movements necessary for being born. Bill needs this initial impulse to carry through his birthing process symbolically.

After being born in hypnosis, he said that he wouldn't have been able to do this on his own. At the moment, he realizes that he has ever needed a man of authority, who gives him an impetus. An excerpt is cited from Bill's one-year inquiry:

"An understanding and elaboration of my birthing trauma were possible in the group. However it seemed yet as a first step... Several events and experiences of my life came to a new light, and what was the most important to eliminate obstacles felt as immobile and unchangeable was set in motion due to psychological work occurred in the tandem hypnotherapy group."

2. DTH with Virtual Twins

At the beginning of pregnancies, 10-30% are considered as twin, but some days or 1-2 weeks later, one embryo vanishes according to research data (Sandbank, 1999). The sign of "Blighted Twin Syndrome" seems unconscious and unspeakable sense of loss, deeply felt despair and rage (Emerson, 1996). We suppose that similar emotions can be felt in the case when the gender identity of the fetus is the opposite as expected by one or both parents.

We have known Bill as his life is full of failed things. His virtual mother–son tandem hypnosis was already mentioned. Later in the course of the group

process he took part in virtual twin-type tandem hypnotherapy with a 60 year old lonely woman named Betty, whose grandmother had died very early, and after her mother delivered her divorced soon. Both her mother and she were orphans as her matrilineal message would be: "You have to survive alone!" When going into tandem hypnosis, they were sitting back to back supporting each other (by touching each other's back).

The therapist felt Bill tense, so he asked him how to feel. Bill claimed that he wanted to share this place with nobody, he was disturbed by the appearance of his imagined twin-sister, and he wished to possess his territory alone by his right. The therapist asked him to thank his twin-sister for sharing in her place. At the moment, Bill relaxed and began to smile. Then his symbolic being born happened spontaneously without the therapist's helping intervention. Here is an excerpt from his diary:

"I was disturbed by Betty's joy. Why she so happy is if this is no place for her at all! The resort is mine! My anger began to resolve when hearing the suggestion to thank her for having entered me here. I guessed that she also had the right to exist, and she would have had the right to protest against me to have been here, but she didn't do so. Why am I such angry and selfish?"

While being in tandem hypnosis, Betty felt joy and floating in a sunny space close to Bill as if two beans in the uterus. After she imagined being born, she felt moving happiness, and in a strange way of her, laughingly, she wanted to caress Bill's head as if she imagined brother's tiny round head.

3. DTH with Virtual Mother and Daughter

In this tandem trance, two women, members of the group took the role on the one hand, of a virtual mother, and, on the other hand, of a virtual daughter. The daughter's part was of Alice, who had social phobia and depression, and the mother's one was Charlotte, who sometimes had anxiety attacks. Some parts of their family's history seems being impressive to be cited here.

Alice's great grandmother arrived from the Balkans to Southern Hungary to try her fortune, became pregnant, and was rejected by her environment has given birth to Alice's grandmother out of wedlock. She died at the age of 24, in shame, as the family legend goes. The daughter, Alice's grandmother, was a dependent, helpless person all her life, also giving birth to a child, Alice's mother, out of wedlock. As a child, Alice had to care for her grandmother and mother, who both suffered from being regularly sick in the street due to their agoraphobia and panic disorder. Alice's mother showed some talents, and she also found a kind husband, but the matrilineal heritage of "women are always losers" did not let her abilities become manifested; she became ill, developed anxiety–depression disorder, which was followed by cancer, and died after a long period of suffering. Alice developed severe psychosomatic illnesses twice in her adolescence, possibly as a manifestation of the matrilineal "curse", and she was forced to give up her career as an artist.

The second participant was Charlotte, whose grandmother married the man she loved, gave birth to Charlotte's mother, then died in tuberculosis at the age of 24. The mother was brought up in an emotionally cold climate and later gave birth to Charlotte with whom she had a disharmonious relationship.

Before DTH Alice, "the daughter" was lying in "the mother" Charlotte's lap. During hypnotic induction, expression of tense can be seen on Alice's face, who was asked by the therapist about her feelings. Alice said that they were in the uterus with Charlotte, and she felt sad, which was located outside the uterus. Then the therapist made Alice imagine a good fairy who was capable of using charm sunshine be in the womb.

After tandem trance, Charlotte reported that when she had entered into the womb, she had seen rolling darkness and had felt endless sadness could have come from Alice's mother. Despite of good fairy's efforts, this endless sadness, was only temporarily resolved. Returning to the tandem hypnotic session at the moment when Charlotte felt this sadness she began to swing on the side of Alice as a mother rocking her baby. Alice had burst into tears and laughter at the same time. After tandem trance, she said that sadness was resolved with this burst of tears and laughter. Alice felt that she had someone, who was accepting and loving her, who didn't keep her own feelings more important than of Alice. Finally, Charlotte said that she received and hold Alice's emotional needs during tandem hypnosis.

In a two year inquiry, Alice reported that symptoms of her social phobia were relieved, and Charlotte wrote about a better relationship with her mother and daughter, whom she more accepted than ever.

4. DTH with real twins

Here we report on the case of a 27-year-old lady (gymnastics trainer), Nancy, who explicitly sought hypnotherapy. She gave birth to two children, and it was after the birth of the second child when she began to suffer from irrepressible obsessions. These included fears of not being able to swallow automatically, or of not being able to articulate words, or automatically breathe. Furthermore, she had a fear of going mad, or blind, and a fear of objects exploding the minute she would look at them, that is of unintentionally destroying the world, and others. All these fears emerged in the presence of retained reality functions, that is, as totally bizarre recurring thoughts. Nancy was born in a small country town from a twin pregnancy. Her twin sister, let

us call her Judy here, had an immature personality and conducted a self-destructive lifestyle. She didn't finish her schooling and gave the impression of an unborn fetus living up her resources greedily without a need for compensation.

The girls' father, a car mechanic, was a rigid and violent man dominating the whole family, by keeping those who challenged him under control with drunken abuses. He continuously physically abused all her daughters. His small business had been successful, and he had always used excessive control over his wife and daughters. Later he developed Parkinson's disease, which can be regarded as a symbol of the extension of his exaggerated psychological inspection to the control of movements and died.The mother was a submissive woman who worked as a shop assistant, and who was living like a little mouse in her introverted world. She acted as a subordinate to her husband and was always willing to be dictated and arbitrarily commanded by him. In the business, she was in charge of taking orders, handling the customers.

The girls were looked after by relatives, in line with the father's will. Nancy has clear memories from the time when she was between one and two years old, explaining to Judy that the uncle was unsuitable and so had to be hated out. And that's how it happened until a pedantic aunt turned up who met their expectations and who looked after them as late as their teenage years. Nancy remembers clinging to the aunt's skirt, begging her not to leave the house because she was dreading the return of her unyielding father from work. When the aunt unexpectedly died, they were twelve years old. The new helping lady (a neighbor of them) seemed to ignore the rules of hygiene, and Nancy began to develop a disgust towards her. She refused to eat, lost weight, and had to be hospitalized on suspicion of acute colitis. Nancy, who had been a self-assertive person, controlling her environment and putting herself into the center, already from a young age, was increasingly becoming compulsively accurate, a perfectionist who excelled with her achievements both in academic subjects and in sports.

As if to offset her aggression, she supported and patronized those close to her, making them her twins, so to say, and organizing their lives. With Judy, she did the same. Despite all Nancy's achievements, it was Judy who received more acknowledgment from the father. Her first anxiety state developed when she was sixteen, and she has had anxiety states accompanied by the symptoms of the stiff neck ever since. After being physically abused by the father at the age of sixteen, Nancy moved out of home and has never returned. She feels disgust with any object coming from home and sees it as a source of "infection." This sense of disgust has extended to her mother, rendering their relationship permanently tense.

Judy's life has been hit by even turbulence. She refused to obey her father's will, struck up relationships with men of dubious background, used drug, and alcohol, did not finish her schools, and has lived in poverty, relying on casual work. As Nancy's and Judy's mother's history: she was an unwanted child raised in a cold and achievement centered family climate, receiving little love. This handicap was able to compensate for a life of hard work. When she became pregnant, her husband proclaimed that they were to have no more than one child. The twin's mother never thought of having two children. After the delivery of the twins, she could not breastfeed and the babies showed symptoms of prenatal stress as excessive screaming, apathy, less sleep, increased irritability, states of extreme restlessness (Janus,1997; Sandbank,1999).

During her intrauterine regressive hypnoses, Nancy reported on the following experiences: While she was perceived herself as an embryo only a few millimeters long, she suddenly noticed a formidable creature occupying the whole space, which was there motionless, and it was impossible to know whether it was dead or alive. Maybe Nancy's conception is considered as a superfetation some weeks after Judy's conception.

In the therapy, Nancy started to feel anxious, and by using her adult cognitive operations, she realized that she suspected that perhaps the others were not aware of Judy. It was her who had to raise her mother's attention by foretelling, so to say, that "Mummy, there are two of us." During hypnosis, she noted in despair that she did not succeed in this. When her twin turned to face her, she looked disgusting and frightening. In an awake state, Nancy associated this feeling with her disgust relating to the mother and the home, a womb symbol. In the hypnosis, she lived through how the space available for her was becoming less and less as they were growing, which finally forced her into a pose in which her back was stretched backward, a feeling that might have been the underlying cause of stiff neck. She felt to be responsible for keeping Judy alive, and this was why she had to help her in getting born. This feeling might be the reason why Judy was to be come into being first. At this point in the hypnosis, Nancy felt that she was able to stretch out and relax at last, as she had to stay on to become mature enough to be born.

However, the gynecologist insensitively reached into the womb, seized her leg, and her protestation notwithstanding dragged her out into the open. She saw two gynecologists, a young one and another who had white hair, a description which was later confirmed by the mother. Here in the therapy, Nancy's obsessions had become more intense, while actual distress elicited a feeling of shame and social phobia. At this point, her mother and sister began to be included in the DTH sessions. In the joint tandem hypnosis with her mother, Nancy was reassured that she was not responsible for

the fact that Judy was not expected. In contrast, while the mother could experience that at a deep psychological level, she had indeed been aware of having twins and had been looking forward to having them. Judy, like Nancy, exhibited high hypnotic susceptibility and was able to live through intrauterine experiences as early as her first individual hypnosis.

Judy reported on elementary sensual experiences, such as the velvety stroking of the amniotic fluid, its viscosity, particular taste, the waves which caused vibration on her skin, and enabled her to communicate with Nancy. When noticing that somebody else was also in the womb, she got surprised, not knowing first what it was, then she swam over to it and found her cute and wanted to play with her. On the therapist's suggestion,Judy chose a guardian spirit, a dolphin, who helped her get born by leading the way and exploring the birth canal, and Judy followed the dolphin. When she was born, she sent the spirit back to help Nancy, too.

In the course of Nancy's and Judy's mutual tandem trance, Nancy kept being passive, letting her twin take the initiative. Later Nancy explained that she would have had a contemplative nature had the intrauterine context not demanded activity from her; the organizing and governing of other people's life as a gymnastics trainer at a High school. Judy, on the other hand realized that she had to initiate contact with her mother if she wanted her to know about her existence.

During the next therapeutic session, all three of them got into a trance. To transcribe stressful experience, they attempted to live through every single event in the most natural way. It was very exciting to see how – in the wake of a therapeutic intervention following they're born – they jointly recollected events of their lives at 2, 5, 10, 20 years of age, in the spirit of positive change. During a future pacing, Nancy was preoccupied with her school-age children, while Judy, wearing an elegant costume, was organizing some company events on her mobile.

As the treatment centered around Nancy's problems, we would like to give a short account relating to the interpretation of her illness. The precise etiology of the obsession was revealed in the executed DTH sessions. According to Roland Fischer, thinking is rooted in movement, as he put it an experience of moving is the moving experience (Fischer,1986). This idea gets support from the fact that the neural pathway of thinking and movement control is equally the circuitry of cortex-thalamus-cerebellum, the subcortical section of which is already in operation in the fetal phase. It is logical to assume that self-generated movement can only be designed by anticipating its outcome. What was the course of development concerning the interaction between Nancy's self-generated movement and "thinking" when she was around ten weeks old after conception? As she was growing, her motivation to move was increasingly hindered by the presence of Judy. In the joint tandem trance involving Nancy and Judy, Nancy's feeling of being pushed out was successfully overwritten by an intervention suggesting that the fact that the mother knew about Judy's existence meant that Judy had a right for being, so she did not need to take over Nancy's space to call the mother's attention to herself. On an unconscious level, the mother expected two babies, which meant that Judy and Nancy equally had the right for being.

Nancy must have had doubts not only concerning the hindrance of her movements but also as to her right for being. "So, who is it now, who exists, who has the right to being, she or me? Am I supposed to move at all? Can I show the signs of living? May I call attention to myself, and do I deserve to live at all, or should I quietly let her take away resources and die?" This grave doubt is still manifest in her existential anxiety, and in her obsessions, sense of disgust and social phobia. Her constraints revolve around life and death; "Can I breathe, that is move?, Can I speak, that is communicated?, Can I and am I permitted to live?, If not, may the world be destroyed, may everything I look at exploding, including Judy!". Murderous aggression possibly elicited instant guilt and through reaction formation caring, love, as demonstrated by her overprotective behavior. At the same time, her rejection of the womb carried a kind moral judgment, as if saying, "I reject you as you have not acknowledged my right for being!" (Seguí,1995).

A hypothesis based on evolutionary psychology provides us with further insights contributing to the interpretation of aggressive urges. Following MacLean's idea Ricarda Müssig (1995) put forward the proposal that the first trimester is characterized by the territorial instinct domain of the fish–reptile phase in phylogeny. The baby reptiles, following a short period of maternal care, acquire a territory of their own, attacking and killing strangers transgressing the territory's borders even if coming from the same brood, or alternatively, they flee away. Then in the second trimester, the emotional bond which is being formed between mother and fetus makes the murderous aggression and persecution anxiety of the reptile phase to be overwritten. However, the dramatically intense impulses may stay on at the most primitive level of the mind's functioning like fossils to be integrated into an unconscious dynamic representation of an expectation suggesting that the important other would relate to her or him in a similarly exploitative or persecution manner. This hypothesis offers an alternative interpretation for the disgust Nancy felt, namely as an emotional self-reflection on archaic hate stemming from the fetal reptile phase (Share,1996).

After DTH finished, individual psychotherapy was continued. During three years course of the therapy concerning the symptoms, it displays a fluctuating course with a strong tendency of improvement. Nancy's

obsessions, stiff neck, and social phobias still appear in stress situations, but she has increasingly more effective means to overcome them. Now she is symptomless. Her relationship with her mother has become more harmonious, and her sense of disgust towards her has considerably diminished. No doubt, her personality has become more mature, her handling of aggression, her empathic skills have both improved while her need to control others and her perfectionism has lessened. She has become more open to emotionally mutual relationships than she was before. She would simply like to become an emotionally harmonious and contented woman and is eager not to pass on the gloomy intrauterine experiences which she integrated into her character.

IV. Discussion

According to the Turners' "Emotional DNA Theory" (Turner & Turner-Groot, 1999) it is postulated that in cases of turning points of course of pregnancy, from the beginning of conception via invasive interventions, i.e. amniocentesis and complicated delivery to intensive perinatal care, every positive or negative thought, emotion, wish or act the parents have got relating to the unborn baby are supposed to be built up to the fetus' psychobiological regulation and determines how to cope with stress. The way how to battle with stress becomes an implicit somatic memory as a fractal, which can repeat itself along with life-time either.

The second case seemed to address to intrauterine territorial instincts (Müssig, 1995). It was known that Bill was expected to be born as a girl by his father. If we accept Emotional DNA Theory, this expectation might function in such a way as if Bill, being a boy of his right, would have got an imagined twin-sister. Nevertheless, Bill would have had identified with the female gender role, but that wasn't the case. Thus it was clear to the therapist that positing twin-type tandem hypnotherapy with a woman could recall Bill's early implicit somatic memory of his dubious feelings about his expected gender role. It is what happened exactly. The twin position provoked Bill's jealousy against Betty, his symbolic twin-sister. He felt that Betty wanted to possess his territory in the womb. Bill's usual attitude and behavior is reinforced probably, in his social relationships in a recursive way that he is not good and acceptable enough since he is not a girl. In vain, his activities would be born he wouldn't positively be reinforced at all, and for this reason, he has to act and delay doing something at the same time because of both rivalry and frightening feelings stem from imagined twin-position he has got in his unconscious mind. Tandem hypnosis gave him a possibility to correct his implicit memory: a repeated virtual twin-situation made Bill accept a girl's potential appearance close to him in social space in the way of neither being threatening nor rivaling him.

Betty lived her own life alone, sharing her intimate emotions only in a few friends. During twin-type tandem hypnosis, she relived experience of oneness with Bill as if they would have been two beans close to each other. This experience moved her so much that it seemed as if she wanted to flood Bill with all of her unfulfilled wish and love. Betty wasn't disturbed by Bill's anger and jealousy at all, which probably means that she corrected partly destructive authority and invisible loyalty of her mother and grandmother, which based her female fate on.

The third case is viewed as an illustration of how can destructive trans-generational messages be elaborated by virtual mother-daughter tandem hypnosis. Alice has yet never realized that sadness and mourning don't exist inside her, but they are outside in her ancestors' life. Therefore the matrilineal heritage can't be considered as her fortune. Thus, the trans-generational message: "You couldn't be who you are!" can be eliminated, and her social phobia was relieved.

The difference in efficacy between individual and tandem hypnotherapy (Bányai, 1998) can also be seen in the way how Alice's imagined rolling darkness became resolved. It is obvious that the suggestion of a good fairy's sunshine in the womb, which couldn't be considered as effective therapeutically, is viewed as the same technique as used in the frame of individual hypnotherapy. To make the difference, tandem hypnotherapy gives a possibility by the tandem partner's physical appearance, who is capable of resolving the patient's unbearable emotions by his/her direct feelings and acts, as happened in the third case.

Consequently, your mind can remember fetal stress situations when faced with regulatory dysfunctions similar to those in the fetal condition (Dowling, 2002). The impact of the traumas suffered in the fetal phase is shown to be the incorporation of the fetus' response to stress into its regulative processes, its coping system, and, in particular, into its coping with stress, with a consequence of deforming or modifying them (Bergh, 2002). Severe or recurring traumas such as attempted abortion or neglect might result in the structural damage of the brainstem and the limbic system and in synaptic pruning, which results in reduced synaptic connections among the various areas of the brain (Schore, 2003). These damages may then be manifested in extra-uterine life as chronic deficiencies of psycho-autonomous regulation, in somatic illnesses, or in psychosomatic and mental disorders, as illustrated using the fourth case (Siegel,1999).

Implicit memory seems to be characterized by a fractal or self-similarity principle, whereby it can be repeated and multiplied at the various hierarchic levels of personality functioning. Fractal refers to an organizing

principle of your emotional and cognitive processes, characterized by a capacity of creating unconscious working models, with which you will be primed towards future experiences by experiences not yet consciously lived through in the past outside the womb; which results in the fact that "you can remember the future," so to say (Fedor-Freybergh, 2002; Stern, 2004). By implicit memory, the mind remembers the early stress situation in such a way that the actual stress situation precipitates the original visceral–somatic dysfunction, which was brought about in the fetal age by the damage.

In this sense, implicit memory represents a defective mechanism of self-regulation relating to the historical and relational dimensions of human life, which activates identical deficient processes in all situations, which are analogous with that in which the original damage occurred. For example, when prolonged labor complicated with suffocation has formed the base of implicit memory, the memory might be evoked later in distress situations either as fear of suffocation, or cardiac arrest or panic attack or agoraphobia. As a matter of fact, agoraphobia can be regarded as suitable to be an implicit or bodily memory of coming out of the birth canal to the threatening open space of extra-uterine life. Also claustrophobia can be seen as the implicit memory of the fear of being locked into the narrow and engulfing birth canal (Gabbard, 1994). Actually, this tendency for the pattern of turns of life to be repeated again and again along the lifespan is called recursion, since these patterns have been engraved into your body and mind through the mother–fetus bonding during the intrauterine phase (Share, 1996).

The theoretical framework of the previous case vignettes may be based upon multifaceted experiential and meaning dimensions of touching. Touch is said to be "the mother of perceptions," and the first language (Montagu, 1986). Tactile mode of perception has been functioning before the central nervous system would develop. It is the reason why conscious memories of touch experiences originated from the embryonic period of life couldn't be available. However, these touch experiences are maintained as implicit somatic memories by skin receptors. Moreover, they are supposed to build up to somatic and nervous regulation of the embryo's developing organism. This regulation might be viewed as a specific pattern of stress-coping processes, which may be repeated when facing new stress situations along with life-time either.

During tandem trance, a mutual physiological, emotional, and experiential attunement is established between the participants in tandem via mirror neurons and adaptive frequency oscillators as stating by scientific researches (Bauer, 2010; Dash, Hebert & Runyan, 2004; Righetti & Alii, 2009). The hypnotherapist prompts a specific division of attention, whereby the participants in a trance, instead of focusing their attention on themselves, focus on the "meeting points" of their observations. The therapist builds upon the experiences that originated from joint bodily communication, creating calmness, warmth, and security. This way, mutual emotional and experiential focus will be developed, which can lead to a sensorimotor attunement between the tandem participants via touching each other (Vas & Császár-Nagy, 2013a & 2019).

Meanwhile, reading the text, you can take up the question of whether fetal consciousness exists.The human organism is capable of making several kinds of systems work based upon physical, chemical, biological psychological and, social self-organization (Wilber,1996). Nowadays, researchers' attention is being directed to the order of subatomic, nano-scale systems (Bókkon, 2005 & 2009). Supposedly, an embryo, even in an early phase of development, can emit such coherent resonances generated by means of bio-piesoelectric crystals by which she/he could send information to those cells of the maternal organism which contain special crystals – those in the hypothalamus, epiphysis, ovary and so on. Excited cells can, on the one hand, trigger a conversation of neuroendocrine regulation in the maternal organism, and, on the other hand, they can react with resonances of specific characteristics. The aim may be a functional attunement of the two organisms both to undue the genetic program in an environment–dependent way and to build up the fetal constitution (Vas, 2013a & 2013b; Vas & Császár-Nagy, 2013a & 2013b).

In other words, the beginning of our existence can be considered a sort of joint resonance, tuning to each other not in a material sense but terms of wave-resonance. It's probably not by chance that the skin has mechanoreceptors able to detect sound pressure spreading in amniotic fluid. Fetuses can hear by their skin before their cochlea evolves. Mind you, the human organism can create more and more complicated structures to detect physical resonances.

To engender seems to be an eternal mystery of body-soul unity. To be conceived is analogous with spiritual conception (refers to the verb "incarnated"). An essence of mother–fetus interaction is considered to be a specific human relationship to be created, and in the course of this interaction, a human being can be transmitted from a biological to a spiritual dimension. The aim of this interaction is two-fold: on the one hand, to provide energy for fetal regulative processes to maintain a balance of organization to build organs, and on the second hand, to give information as to how the control has to take place and how the genetic program has to be undid. The flow of information and energy is secured by the neuromodulatory system.

No one knows what happens during the conception of a fertilized ovum at a "subjective" level. You can evoke cellular and fractal memories which, supposedly, are different designations of the same

processes. However, they can not be brought into consciousness since they can be re-lived at a symbolic level only. All of the cells from a later evolutionary stage in the human organisms are engendered from the single zygote. Thus, we inherit the zygote's experiences using the genetic memory since our implicit or fractal memory is used to re-live the formal pattern of previous occurrences at an unconscious level (Laing, 1962). So, an experience gained can be re-lived again and again using the fractal memory. Illustrative examples of this are when children re-live their birth by playing hide-and-seek or when an adult individual can re-live his/her premature birth unconsciously each time he/she leaves things unfinished or half done (Janus, 1997). So, you can "remember to future" due to fractal memory, which inform us of the past (Siegel, 1999).

Ontogeny repeats phylogeny in some respect; therefore, it seems logical to go back to the unicellular state of your existence. More and more researchers think that a fertilized human egg has a "self-conscious journey" through the oviduct to the womb, to find the best possible place for implantation (Piontelli, 1987 & 2010; Seelig, 1998, Verny, 1995). That kind of biophysically/chemically controlled awareness reminds us of the behavior of protozoon used to live in the Archaic Ocean. Before someone would say that this is far from the reality of a zygote's wandering let's ask ourselves the question: why is it that many cultures isolated from each other in place and time describe, in their myths and tales, a hero's journey from the beginning to the consummation with the same turns of phrases? (Janus, ibid, p. 163.).

It can be assumed that a hero's wandering in myths and tales means such a symbolic concentration of different dimensions of objective and subjective realities that can be likened to condensation of dream-work (Freud, 1985). After all, the sense and aim of a symbol's emergence are to connect matching subjective and objective elements of reality. We might say, as an objection, that the fetal ultrasound technique can detect and explore only the developmental and behavioral processes, which can be monitored from the outside. That's true, but having said that, nobody conclude the conclusion that a fetus could not have awareness. In Ken Wilber's opinion (2009, pp. 80-84.), what the ultrasound device can experience is an objective outer quadrant of reality, rather than the subjective inner quadrant representing individual consciousness or the collective intersubjective dimension of cultural symbols.

There are such psychotherapeutic methods during which a client can re-live his/her conception, accompanied by ecstatic experience (Share, 1996; Wilheim, 1998). Whether only the phenomena observable in an objective way could be considered real? – the question is raised. The first phase of the struggle for life is the zygote's implantation (Chamberlain, 1993a & 1993b; Fedor-Freybergh, 1996a, 1996b & 2002). An immune coalescence and war have begun with that event. On the one hand, this phase can be regarded as a sort of coalition between the mother's immune system and the fetus by using such resources, for example, as releasing choriogonadotropin hormone to maintain the required maternal progesterone level so that menstrual cycles be put on hold. On the other hand, it is a struggle of the maternal immune system against the zygote, with the latter being treated as a partly foreign body by the mother's organism that is trying to push the zygote out. This is a life-threatening struggle for the zygote to avoid annihilation.

However, in such cases, when fetal development is in danger, the placenta depletes the mother's organism of nutrients. If that balancing function of placenta collapses due to toxic, infective effects, or lack of the mother's resources, the fetus' fight for possessing and retaining resources will become more and more useless and its fight to hold and safeguard his/her body and territory will fail. Even if an intrauterine fetal demise does not necessarily occur, the fetus pays a very high and unfair price for survival with possible developmental disorders in the organ systems. At the same time, the mother can also suffer from her state of deficiency, lack of necessary resources by developing diseases like disturbances and malfunctions in the endocrine, circulatory, immune, and neuropsychological systems.

It has been confirmed and supported by recent research data that maternal distress, mainly anxiety and negative emotions make adverse effect on the health of both the fetus and the baby to be born (Bergh, 2002; Blum, 1993; Gordon et Alii, 2010). It is delineated by research studies how deeply an unborn vulnerable baby is affected by the mother's mental imbalance (Hepper, 2002; Hugo, 2009; Huizink, 2000). MacLean's theory (1970) about the human brain has been repeatedly mentioned. According to this theory, the human brain consists of three phylogenetic layers: the brainstem originated from reptilians, the limbic system emerged in birds, and the limbic-cortical region stemmed from mammalians. The way how an embryo's genetically programmed behavior is formed depends on the functions of the above brain regions, that's what some researchers suppose to be a valid explanation, at least (Müssig, 1995). Accordingly, an embryo's behavior is controlled by a territorial instinct program in the first trimester of pregnancy.Therefore she/he reacts to any source of danger affecting his/her territory with territory-protecting, counteroffensive; fight or flight behavior.

Twin pregnancies can be 10-30% of all pregnancies (Sandbank, 1999), but in the overwhelming majority of cases, one of the twins dies prematurely within a short time. So there is a life-and-death struggle in the womb in many cases. For the fetus to be able to fight this battle successfully, the so-called archaic

"mistrust" already mentioned, i.e., the fear of destruction and an aggressive "reptilian behavior" of defending territory are required. In the second trimester, the fetus comes to a closed eyes' state, characteristic of newborn rodents. This phase is characterized by blind trust and care as well as by emotional attachment – a state almost exceeding the territorial horror and cruel aggressiveness controlled by the hypothalamus of the fish–reptile period. The third phase of the rivalry and the coalition between the mother and the fetus can be called a representative period. The stake of that phase is likely to gain bodily and mental unity of his/her own, and to possess his/her subject, i.e. to have got his/ her own self-representation. It looks like the biological communication of a fetus is mirrored in the mother's mental functioning.

It is worth considering Raffai's (1996, 1997, 1998, 1999, 2000, 2002 & 2010) argumentations about how a fetal sense of self is formed by the mother's subjective mirroring. Using that such pattern of interaction is evolved between them that seems "telepathic" in the sense that beyond words uttered, a fetus' behavior and reactions are highly influenced by his/her mother's images, emotions, visions, and expectations relating to her fetus (Cheek, 1986 & 1993).

As to the baby's reactions, the mother embraces them in the same sensitive and reciprocal manner as the fetus does her maternal signals. To gain a sense of self-identification for the fetus, it is fundamental to reflect the existence of the baby by the mother not just as a foreign object but also such a being not identical with her, who is capable of reflecting the existence of his/her self. That is to say the mother has to reflect her fetus as a subject, too (Vas & Gáti, 2006). The evolving self-reflectivity of the fetus is an effect of the mother's mirroring behavior. As an effect of that reflection of the mother, an awareness emerges in the fetus that she/he exists for his/her right while practicing functions of his/her self and for his/her joy. The fetus'reflective function can be identified as a sense of self (Stern, 1985), and the relationship in which that is evolved is called as a unity bond (Dowling, 2002; Krens, 1999). Reflection is considered to be a rather vague concept to name what is happening here: The situation seems to be even more complicated at the level of regulations since any individual pattern of the genetic program to be expressed can only be given via mother–fetus relationship.

The relationship between the mother and the fetus is formed using biological, psychological, and social effects. A healthy mother, whose relationship with her mother might have been attuned from her fetal period, has a good chance of forming a tuning relationship with her fetus as well. That is the precondition to transmit genetic inheritance smoothly. Any kind of trouble to occur in their relationship can derail either the transmission of genetic code, or the optimal building of organs, organic systems, or regulatory functions. Mother's stress appearing as an effect of unfavorable psychological and social issues impact the fetus in an unshielded way because, if the mother can not set the baby at ease, stresshormones can get across the placenta. It has been made clear, through ultrasound observations, that it is not enough for the mother to cope with her stress. If she fails to secure emotional protection for her fetus as well, it continues to be overwhelmed by stress experienced as emotional strain or extreme excitement (Piontelli, 1987 & 2010).

What gives the fetus emotional security is an intimate and lovely caring and togetherness that regulate hormonal processes taking place between them. It is a verified fact today that some modification of the mother's inner state can evoke similar mode of functioning in the fetus. When the mother is happy, anxious, or smokes, the fetus "does" the same. Is this mirroring, or copying? It is a phenomenon somewhat similar to copying a DNA molecule containing genetic code, so essential regulatory processes are transcripted in such cases. The concept of mirroring is not used here because it is misleading since it suggests a passive process. Whereas a copy or, better still, a transcription can be an exceedingly active process on the part of the fetus.

It's highly probable that initially, the regulation of intercellular relations, then the regulative processes like metabolism, circulation, and others, are transcripted within potentialities determined by genetic patterns. The appearance of self-initiated movement seems to be an essential precondition of both consciousness and the thinking process; the latter is to evolve from the control of movement. The fetus is surrounded not by a sort of sterile growth medium or nutrition solution but by a conscious being, the mother. She can exert control over her fetus with her neuro-hormonal functioning and emotions, and even with her thinking. Initially, fetal consciousness is embedded in an unconscious or more correctly in the not yet conscious, i.e., not emergent regulatory processes; then it will be gradually rising from that to become emergent.

These kinds of regulations will survive in the form of vegetative and visceral functions attuned in different emotional states, to the end of our life. They are examples of unity of bodily–visceral and mental functions. Such oneness is likely to be a fetal sleeping position. A response to be given to the question of the emergence of awareness depends on what development level of the neural structures' functioning consciousness is to be assigned to. If Cartesian Cogito ergo sum is our starting point, then conscious phenomenon can exclusively be assigned to the functioning of the left anterolateral part of the frontal lobe in an adult Homo-sapiens. If this is the case, not only

the animals but little children as well will be excluded from its "benediction" or endowment.

If, however, we consider the numerous transitional primitive forms of awareness of phylogeny, we have to accept the possibility that the human fetus can possess consciousness in the earliest possible period. In all probability, this is because, in that aspect, the mother's conscious attention and emotional reflection relating to the fetus secures an exceptionally, ideally favorable possibility or condition for this. Consciousness is regarded to be a relational occurrence, and as such, it is accepted undisputably by both evolutionary psychology and philosophy as well. Therefore, it sounds logical, and also confirmed and supported by ultrasound observations, that fetal awareness, already present at some level of preconsciousness from the very beginning, is considered to be the essence of mother–fetus relationship.

The essential feature of preconsciousness can be related to what is considered to be the reproductive ability of a living being. The nature of reproduction is to transmit information from its own existence to successors. As far as we know, it is unthinkable to do without a DNA molecule (Buss, 2001; Cosmides & Tooby, 2001). This is the crucial difference between a living being and a nonliving thing. Even a protozoon is capable of reproduction, so this is a sort of "trademark" of cellular memory. The other specificity of preconsciousness is supposed to occur in more sophisticated organisms, where and when specific cells get differentiated to regulate metabolism through centralized control of hormone functions. Later, cells with even more specialized processes get relieved from carrying out metabolic functions of a living organism to create the neural ganglion.

Can it be possible that this is the very point at which we find the most important peculiarity of consciousness: the capability to self-reflection? Is this the point at which the passive not-reflected floral existence is separated from a self-reflected animal being? Self-reflection and movement are related to each other in a special fashion. Supposedly, Roland Fischer's (1986) note that relations is pertinent, saying that experience of moving is the same as a moving experience. It is because the neural system to coordinate sophisticated movements is identical with the neural organization responsible for controlling our thinking (i.e., a net interconnecting the frontal lobe, thalamus, and cerebellum). So, could an embryo with evolved musculature and capability to move and change its location be considered a conscious being?

There are several transitional phases in this research area, from the most primitive sense of motion of his/her self to an evolved self-reflection, with the latter the basis of consciousness. A living being needs to be connected to the outer and the inner environments to be able to compare the genetic information with the surroundings, and to facilitate their mutual interactions, accordingly. A prerequisite of that is the emergence of a highly refined regulatory system of energy and information processes called consciousness. It is the kind of regulation that makes possible rise in the degree of freeness of a living being as energy-using and producing system (negentropy), his/her survival, coping with environmental challenges, growth, and reproduction. Biological reproduction transmits information held in DNA about organization of the body, however, it is in a living being's interest to make the information obtained energized, i.e., put into action.

In practical terms, this process is being performed under the operating principle of self-organization, self-regulation, and flow of information, as mentioned previously – a formula that seems to be the most significant one in the emergence of preconsciousness. You can see the way; how a unit of information and energy, i.e., "infoergy" generates consciousness. From our standpoint, awareness from its most primitive manifestational phases to the most complex, sophisticated forms serves one single purpose: to enable a living being to be released from the "predestined fate" determined by natural laws. To put it another way, we can say that consciousness or conscious existence is the ultimate objective or mission of the genetic program itself, so awareness can be considered preprogrammed genetically. Surprising as it may seem, this is the way how Fedor-Freybergh's (2002) notion makes sense, becomes comprehensible. According to this notion, a fetus's awareness precedes the process of building the fetal organism itself, i.e., consciousness precedes existence.

V. Conclusions

DTH sets a frame of therapy, which is similar to the original mother-fetus bond. The implicit bodily memory has a fractal nature. If there was a prenatal stress the same context might be repeated all through somebody's life in stress situations. If it is the case psychotherapy has got a problem solving possibility. Insomuch as social interactions exert a direct effect on gene expression DTH can play an important part in that implicit somatic memory stemmed from fetal trauma be resolved. According to the authors DTH belongs to transpersonal psychotherapies (Grof, 2000). DTH can be viewed as a special hypnotherapy context in which fetal visceral–somatic patterns of experiences leading to later suffering in life can be worked through with the help of the therapist and the co-therapist – a healing team – who can cooperate for the client's benefit.

Authors Note

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Male Body Mass Index and Seminal Parameters

By De Vicente Montes, Lucía, Motato Moscoso, Yamilet, Ortega García, Ana, Calvo Juan, Agustín, Franco Sansaloni, Ángela & Espejo Catena, María Rita

Abstract- *Objective:* To evaluate the controversial association between body mass index (BMI) and seminal fluid parameters of male patients who consulted with their partners in our clinic.

Design: retrospective observational study including 1009 males attended in Instituto FIVIR from January 2010 to January 2018.

The following parameters are registered: height (meter) and weight (kg) in order to obtain BMI (kg/m^2), age, fresh spermatic count (m/mL), progressive motility (%) and normal morphology (%).

Patients: Of 1009 selected patients, only 471 met the inclusion criteria for the present study. All of them were European, white males, who obtained the seminal sample at our center (after three days of abstinence and no history of fever the previous four weeks). When the analysis had to be repeated in the same patient, we included only the first analysis in the study.

Conclusions: In the present study, a BMI increase was associated with a decrease in sperm quality, affecting both concentration and motility. Sperm morphology was not affected.

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Strictly as per the compliance and regulations of:

Male Body Mass Index and Seminal Parameters

De Vicente Montes, Lucía [α], Motato Moscoso, Yamilet [σ], Ortega García, Ana [ρ], Calvo Juan, Agustín [ω], Franco Sansaloni, Ángela [¥] & Espejo Catena, María Rita [§]

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Summary

The association between BMI and seminal fluid variables was evaluated in 471 males who consulted looking for pregnancy. We divided the participants in to four groups: males with low BMI (≤ 18.5 kg/m^2), males with normal BMI (18.5-24.9 kg/m^2), males with overweight (BMI 25-29.9 kg/m^2) and obese males (BMI ≥ 30 kg/m^2). Their medical history, daily toxic habits, and data obtained from semen analysis were taken into account. Males with obesity presented a lower concentration and lowered progressive sperm motility when compared to males with normal weight or overweight ($p < 0,05$). There was a negative correlation between increased BMI and seminal fluid parameters.

I. Introduction

Obesity is a chronic illness where there is an increase in body fat. Its prevalence has increased considerably both in developed and developing countries. It is usually the result of an unbalance between calorie intake and output. Its excess leads to high morbidity and mortality rates and to socially significant direct and indirect economic burdens. Body mass index (BMI) is a relatively simple method to measure body fat, calculated by dividing the weight in kilograms by the square of the height in meters, expressed in kg/m^2 (WHO 1997).

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Like every other systemic illness, obesity affects every tissue, including the reproductive system. On the one hand, most published studies up to date have focused on analyzing the impact of BMI on female patients, reporting its negative effect on fertility potential, hormone levels, the increase in the risk of developing polycystic ovary syndrome, anovulation, and poor results after an assisted reproduction treatment (ART) (Pinborg *et al* (2011)).

On the other hand, both male overweight and obesity cause endocrine disorders that can affect reproductive capacity. Some authors inform of a negative impact on natural and assisted conception, while others report similar reproductive results to those observed in males with normal BMI. Regarding the influence of male BMI on seminal quality, studies are more controversial, as this relationship is multifactorial and represented by an altered hypothalamic-pituitary-gonadal axis, peripheral aromatization of steroids to estrogen, decrease in testosterone levels, increase in estradiol levels, decrease in binding of sexual hormones to globulin and an increase in scrotal temperature (Crujeiras, A.B., Casanueva, F.F., 2015). Moreover, there is proove that the accumulation of toxic substances and liposoluble endocrine disruptors in the fatty tissue magnifies these disruptions (Katib, A., 2015; Sermondade, N, 2013).

Some publications have been able to relate the increase in BMI in infertile males with poor spermatic quality (decrease in sperm concentration, abnormal sperm morphology, and decreased motility) in comparison with normal BMI males (Hanafy, S., Halawa, F.A., Mostafa, T., Mikhael, N.W., Khalil, K.T., 2007; Hofny, E.R., et al. 2010). Regarding spermatic DNA integrity, it has not been possible to establish an association between greater DNA damage in overweight and obese males (Smit, M., Romijn, J.C., Wildhagen, M.F., Weber, R.F., Dohle, G.R., 2010). However, some authors have observed an increase in mitochondrial damage of sperm belonging to overweight patients (Bandel, I. et al. 2015).

The objective of the current study was to investigate if the increase in male BMI is associated with seminal parameter quality.

II. Materials and Methods

The present study is a retrospective observational study, where the medical records of 1009

males who consulted in Instituto FIVIR of Valencia were reviewed between January 2011 and December 2018.

The information included was that of patients who met the following criteria:

- ✓ Inclusion criteria: being 18 years old or older, male, weight and height registered previous to obtaining the sperm sample, one spermiogram made at this clinic with the following parameters: spermatic count per ml (million per milliliter (m/mL)), motility (%), normal morphology (%). The conditions for collecting the seminal sample were: three-day abstinence, no history of fever in the previous four weeks, and obtaining the total of the ejaculated fluid.
- ✓ Exclusion criteria: Patients with a medical history of chronic illness that require chronic medical treatment, cigarette, alcohol, and other toxic consumption. Patients with an oncological history who required treatment with chemotherapy, radiotherapy, or testicular surgery.

The seminal fluid parameters and definitions of the spermiogram used were those determined by WHO (2010 5th edition). Hence: sperm concentration ≱ 15 x 10^6/ml), progressive motility (≥32%), sperm morphology (normal forms > 4%).

The classification of BMI was adapted from the World Health Organization's (WHO) (World Health Organ Tech Rep Ser., 2000).

- Underweight - BMI under 18.5 kg/m2
- Normal weight - BMI greater than or equal to 18.5 to 24.9 kg/m2
- Overweight – BMI greater than or equal to 25 to 29.9 kg/m2
- Obesity – BMI greater than or equal to 30 kg/m2

III. Statistical Analysis

The normality of the continuous quantitative variables was evaluated using the Anderson-Darling test, resulting in all of them non-normal. The mean values of the abnormal continuous quantitative variables were compared using the Kruskal-Wallis test, considering a p value of p≤ 0.05 as a statistically significant difference.

IV. Results

During the study period, 1009 white European males between 20 and 46 years old were attended, of which 471 met the criteria (Figure 1), with an average age of 32.8 (SD ± 3.491) (21 – 41 years old). The classification was made according to their BMI, and the distribution was: Low weight or LW (BMI ≤ 18.5) in none of the patients; Normal weight or N (BMI between 18.5-24.9) in 212 patients; Overweight or OW (BMI between 25-29.9) in 193 patients and Obesity or OB (BMI ≥ 30) in 66 patients. Therefore, patients with normal BMI(N) represent 45% of the studied population, whereas patients with excess weight are 55% of the studied population. The characteristics of the population are described in Table 1.

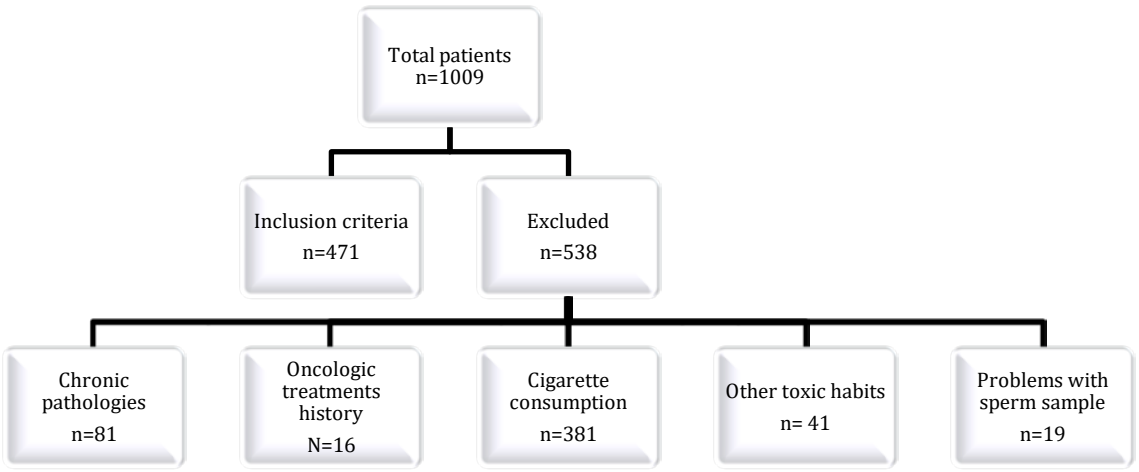

Fig. 1: Flowchart of the study

Table 1: Statistical description of male population with overweight (OW); obese (OB) and normal weight (N)

Variable	BMI (kg/m2) Mean SD (Min-Max)	Age Mean SD (Min-Max)
N (n=212)	22,333 1,552 (19,487-24,977)	32,590 3,341 (22,00-40,00)
OW (n=193)	26,962 1,275 (25,00-29,752)	32,984 3,609 (21,00-40,00)
OB (n=66)	34,249 4,054 (30,043-46,875)	32,803 3,626 (25,00-40,00)

There were no statistically significant differences found for age (Kruskal-Wallis p=0.308) between the groups.

Males with obesity or over weight had a significantly lower sperm concentration and progressive motility than men of normal BMI ($p < 0.05$). Tables 2 and 3.

Table 2: Kruskal-Wallis test in spermatic count (m/mL). P=0.000

Variable	Median	Mean	Standard Deviation
N (n=212)	100.0	111.65	70,39
OW (n=193)	85.0	106.17	73,47
OB (n=66)	39.0	43.09	31,76

Table 3: Kruskal-Wallis test in progressive motility (%). P=0.046

Variable	Median	Mean	Standard Deviation
N (n=212)	70.0	62.71	19,43
OW (n=193)	65.0	60.02	20,63
OB (n=66)	60.0	54.97	23,66

Sperm normality (%) had no statistically significant differences according to the classification of BMI (Table 4).

Table 4: Kruskal-Wallis test in sperm morphology (%) p=0,004

Variable	Median	Mean	Standard Deviation
N (n=212)	5	1.3390	1,3390
OW (n=193)	5	1.498	1,498
OB (n=66)	5	1.699	1,699

V. Discussion

The relationship between male obesity and fertility has been widely described. However, there is a debate regarding the magnitude of this relationship and its mechanisms. On the one hand, various groups of researchers have not been able to establish any or little relation between BMI and a worsening of spermatic quality, as registered by MacDonald et al. in a revision of the most relevant publications (31 studies) between January and February 2009 (MacDonald, A.A., Herbison, G.P., Showell, M., Farquhar, C.M., 2010).

Similar findings were found by Chavarro et al. in the study carried out on 483 males where BMI had no association with sperm concentration, motility, or morphology. Moreover, males with BMI≥ 35 kg/m ^{2} had lower total sperm count than males with normal BMI,

showing that only extreme obesity impacts negatively on male reproductive potential (Chavarro, J.E., Toth, T.L., Wright, D.L., Meeker, J.D., Hauser, R., 2010) mainly affecting maturation in the epididymis and therefore it is considered a poor prognostic factor. Furthermore, males with obesity present an increased risk of oligo and teratozoospermia (Luque EM et al. 2017) azoospermia and alterations in hormonal serum parameters, which show a slight but significant association with BMI, possibly contributing to sub fertility in this population (Bieniek JM et al. 2016).

On the other hand, researcher groups such as Belloc et al. (2014) found a clear association between BMI increase and seminal quality decrease, where volume, concentration, and sperm motility were mostly affected. However, the percentage of normal forms was not diminished (Belloc, S et al, 2014) as opposed to the findings of Oliveira et al. even though they did not find an association with an increase in DNA fragmentation (Oliveira, J. et al., 2018).

In the present study, more than half of the males included (55%) suffered from obesity or overweight (14% and 41%, respectively). This data is similar to that found in a recently published article where 60.9% of the general Spanish population suffers from these conditions and, in comparison to preceding data, shows an increase mostly in males (Aranceta-Bartrina J., Pérez-Rodrigo, C., Alberdi-Aresti, G., Ramos-Carrera, N., Lázaro-Masedo, S., 2016). Such data is even more significant as amongst these men, there is a 50% higher probability of presenting infertility when compared with healthy weight males (Phillips KP, Nongnuj T., 2010).

The average sperm count was lower in patients with overweight and obesity, this is in accordance with previous studies where there is up to 20% fewer spermatozoids when compared to males with a healthy weight (Du Plessis, S. S., Cabler, S., McAlister, D. A., Sabanegh, E., & Agarwal, A.,2010; Nicopoulou SC et al. 2009). Motility was similar to that found in other studies, with a decrease in patients with obesity, hence showing an association.

Therefore, some of the characteristics in the spermiogram could vary depending on body weight, which in turn has an impact on male fertility.

Study Limitations

Our study presents the following limitations: small sample and its retrospective character. Broadening the sample in a prospective study could help define more precisely the relationship between body weight and seminogram alterations.

VI. Conclusions

In this study, there is an association between overweight and obese patients and a decrease in seminal quality, which mostly affects sperm count and motility with a higher frequency than in patients with a healthy weight. However, these statistically significant differences found in fresh samples were not found when comparing sperm morphology.

Therefore, given the adverse consequences of obesity and the possible detrimental effect of male BMI in assisted reproduction treatment outcomes, the benefits of reducing body weight should be discussed when counseling interested couples in fertility treatments.

Conflict of Interests

Authors declare no conflict of interests.

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Effects of Physical Activity on Patients with Chronic Kidney Disease on Hemodialysis: A Systematic Review

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Abstract- *Objective:* Analyze through a systematic review of the effects of physical activity on hemodialysis patients.

Methods: The study followed the proposals of PRISMA (Preferred Reporting Items in Systematic Reviews and Meta-Analyzes). The search for articles took place on the digital platforms Medline, Pub Med, and Sports Discus, from February to October 2019. Itwas found using word combinations specific to the research theme, and they are aerobic exercise and renal insufficiency, aerobic exercise and dialysis treatment, strength training and renal insufficiency, strength training, and renal insufficiency.

Results: 43 articles were identified. However, in the search criteria, 39 were excluded. No studies were excluded by checking titles and abstracts. Finally, four of them were selected for a full reading. After eligibility, all four were included for the final analysis. The PEDro scale identified a high methodological quality of the selected studies. The studies showed significant improvements in the neuromuscular, cardiovascular, cardiorespiratory, biochemical, and organic systems. In addition to improvements in the evaluative aspects of quality of life.

Keywords: *physical activity; hemodialysis; chronic kidney disease.*

GJMR-F Classification: *NLMC Code: WJ 378*

Strictly as per the compliance and regulations of:

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Conclusion: We can say that the use of a physical activity to help patients with chronic kidney disease on hemodialysis, guarantees benefits in functional capacity, whether using aerobic training or combined training.

Keywords: physical activity; hemodialysis; chronic kidney disease.

I. Introduction

Chronic kidney disease (CKD) occurs when there is kidney damage resulting in slow, gradual, and irreversible loss of kidney functions. The CKD can also be called chronic renal failure[1]. In Brazil, the number of patients with his type of pathology who underwent treatment increased from 122 thousand in 2016 in a survey carried out by the Brazilian Chronic Dialysis Survey [2]. The number of people who managed to have a kidney transplant reached 5.7 thousand, a number that has been growing 10% every year[3].

The kidneys are the organs that filter all nutrients and other substances processed in the body. What is beneficial for the body is used and offered for organic demands, and what is harmful is eliminated in the urine. These organs are of great importance, as they are the ones that make the metabolic and hydro electrolytic balance of the organism 1-4. The kidneys also play another role: the release of some hormones into the blood. These hormones regulate blood pressure, make red blood cells, and strengthen bones [5]. The repercussions of CKD associated with hemodialysis treatment can lead to the loss of components of physical fitness that results in decreased functional capacity and mortality in this population[6-7-8]. The CKD patient has several changes in their bodies. Muscle loss is noted, characterized by musculoskeletal changes, which occur at an accelerated rate. This loss occurs due to a sedentary lifestyle, obesity, nutritional imbalance that occurs in conjunction with the reduction of protein synthesis and insulin resistance, two metabolic changes[9].

Another change noticed is the constant fatigue, where the patient has tiredness and lack of energy to perform the most common activities of daily life. This fatigue can be linked to psychological changes, such as depression, because the patient is away from social life, due to the severity of the treatment, abnormal levels of urea and hemoglobin, due to improper kidney function, nutritional deficits, caused by poor food intake[9].

Bearing in mind that the number of people who develop CKD and that this number has been progressively increasing [10], studies are needed that show the effectiveness of structured exercise programs that benefit this audience.

As a form of prevention, patients should be encouraged to practice physical exercises to mitigate the changes caused by CKD. According to the American College of Sports Medicine[11], individuals affected by chronic kidney disease should perform

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aerobic exercises for 3 to 5 days a week, lasting 20 to 60 minutes continuously. If the amount is not supported, sessions of 3 to 5 minutes should be performed intermittently, to accumulate 20 to 60 minutes per day. Resistance exercises should also be performed two to three times a week, with at least one set. This series should contain 8 to 10 movements, covering the main muscle groups. The number of repetitions can vary from 10 to 15.

Knowing the importance of the practice of physical activity in the prevention of diseases, patients affected by some kidney injury should be encouraged to physical activity, which is a possibility to mitigate the changes caused by the disease and by the treatment of hemodialysis or peritoneal dialysis itself, slowing the progression of the disease[12].

A study carried out with patients undergoing hemodialysis performed aerobic training and found benefits such as a decrease in resting heart rate (HR), systolic and diastolic blood pressure (BP) at rest, reduced body fat, and triglycerides increased cardiovascular resistance and reduced platelet aggregation. The study also showed benefits with resistance muscle training such as increased strength, power, and muscular endurance, in addition to providing an improvement in the performance of daily activities such as getting up from a chair and climbing a ladder[13].

However, studies related to physical activity with individuals with CKD are scarce, which consequently generates a relevant limitation regarding a subject that has a demand for more information and consistent directions. Therefore, the objective of this study is to conduct a systematic review of the effects of physical activity on patients on hemodialysis.

II. Methods

a) Search strategy

The structure in this study followed the proposals of PRISMA (Preferred Reporting Items in Systematic Reviews and Meta-Analyzes)[14]. Studies that analyzed the effects of physical activity in chronic renal patients undergoing hemodialysis will be considered for this review as well as both sexes in adulthood.

b) Eligibility criteria and study selection

To compose our study, the search for articles took place on the digital platforms MedLine, Pub Med, and Sports Discus, between February to October 2019. Also, the following criteria were considered: studies with interventions performed on humans, available and free of charge, classified as clinical trials. The articles were found by words combinations to the specific research topic, and they are: “aerobic exercise” and “renal insufficiency”, “aerobic exercise” and “dialysis treatment”, “strength training” and “renal insufficiency”, “strength training” and “renal insufficiency”. Also, the references of all selected articles were analyzed.

The selection of studies was carried out by two independent people who, in case of disagreement, sought a consensus. The evaluation consisted of a selection of studies using the analysis of the title, followed by the analysis of the abstract and the analysis of the full text. With the disagreement between the two evaluators, a third party will be asked to complete the process. The relevant articles were obtained and evaluated by the inclusion and exclusion criteria described below.

Articles that presented intervention methods other than physical exercise were excluded; those who underwent training with non-dialysis patients. And articles that applied physical activities and that found benefits for patients with CKD on hemodialysis were included.

c) Risk of bias in individual studies

To assess the risk of bias, the researchers carried out an analysis of the methodological quality of the studies. The evaluation instrument for the selected studies was performed using the PEDro scale[15]. The PEDro scale is considered an appropriate tool in systematic reviews for qualitative analysis of quantitative studies. The method consists of component classifications for the following categories: selection criteria, the equation between groups, data collection methods, outcome factors. The components were classified into 0 (not identified) and 1 (identified). Studies with PEDro scores between 6 and 10 points, 4 and 5 points, and 0 and 3 points were considered high, moderate, and low quality, respectively. All disagreements regarding the classification of PEDro scores were resolved by a consensus discussion among the reviewers.

III. Results

a) The selection process of articles related to research

As a way of elucidating the research, a process was carried out to identify all possible studies, which could contribute to it. After searching the scientific databases (Pub Med., MedLine and Sports Discus), screening was carried out by checking the title and the summary of the studies found. Those who did not fit the survey were excluded. The studies went through an eligibility process, where all of them were read in full. Because of this, some studies were excluded, taking into account their methodological quality, according to the standards of standardization of the PRISMA scale (Preferred Reporting Items in Systematic Reviews and Meta-Analyses).

After using the keywords, 43 articles were identified. However, in the search criteria, 39 were

excluded. No one was excluded by checking their titles and abstracts. Finally, four studies were selected for reading in full. After eligibility, the four were included for the final analysis. The summary of articles, in table 1, was based on a structured questionnaire that considered the following items: Authors, year of publication, sample (quantity, sex, and age), training protocols, dependent variable, results.

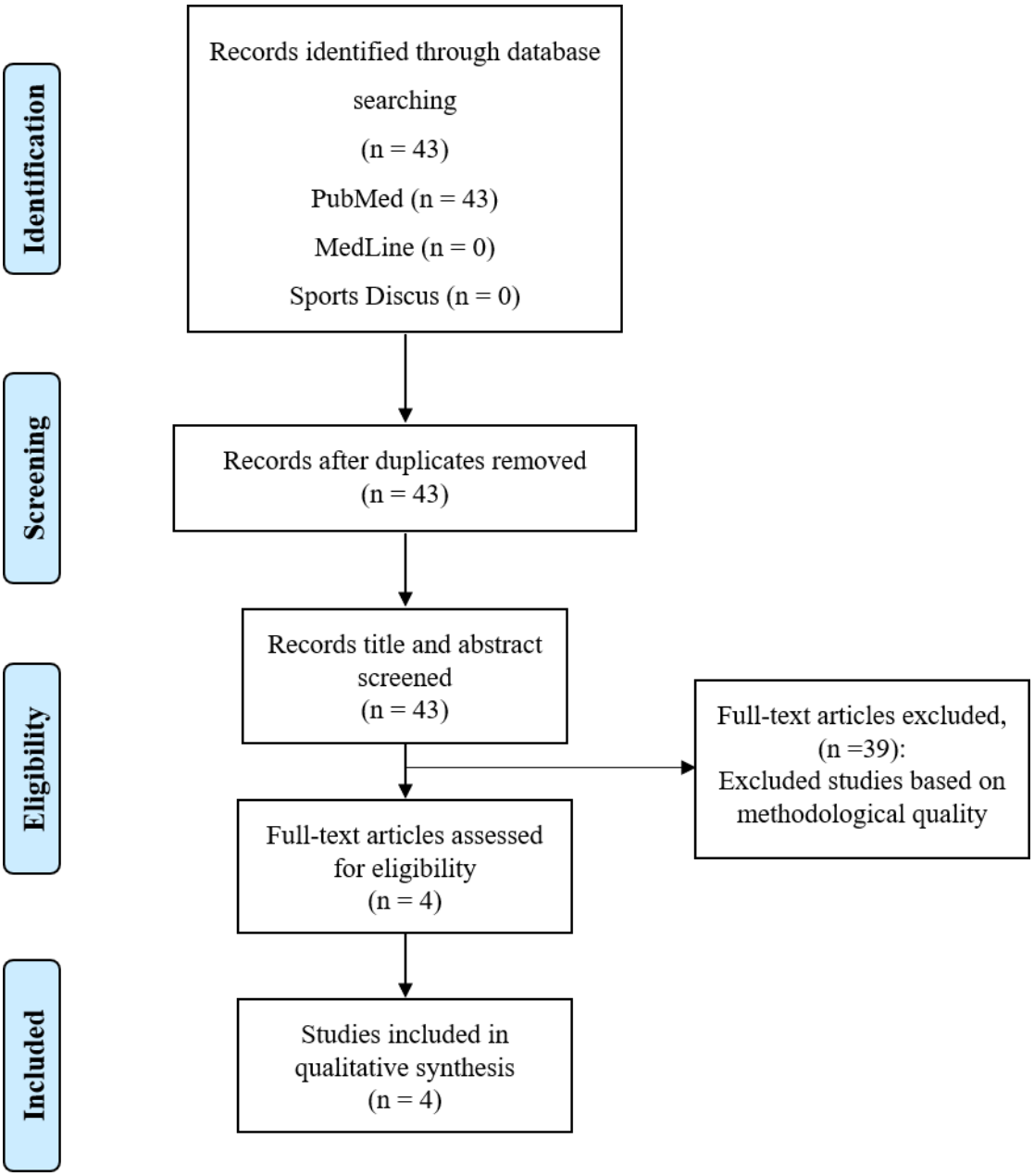

Figure 1: Flowchart of the selection process for articles related to research

b) The methodological quality of selected studies

The average PEDro score for the studies included in the review was 6.25 ± 0.5 points, ranging from 3 to 6 points (Table 1). According to the established quality criteria, the average quality of the studies included in this review is, therefore, high. Also, there was no high degree of variation in quality between studies. All studies [16-17-18-19] met the eligibility criteria. (Question 1 of the PEDro scale) and outcome measures. Likewise, all of them [16-17-18-19] performed a randomized crossover design (question 2 of the PEDro scale). Only one study 16 concealed criteria (question 3 on the PEDro scale). All studies[16-17-18-19] showed similarity between groups (question 4 on the PEDro scale). None of the studies presented blind methodological criteria (questions on the PEDro scale 5, 6, and 7). All studies[16-17-18-19] showed results in more than 85% of the sample (question 8 on the PEDro scale), fulfilled criteria 9, related to the intervention condition (question 9 on the PEDro scale), showed statistical comparisons between

groups (question 10 on the PEDro scale) and provided specific measures and measures of variability (question 11 on the PEDro scale).

Table 1: PEDro score of methodological quality for included studies

Studies	1	2	3	4	5	6	7	8	9	10	11	Totality
Headleyet al.. (2014)	1	0	1	1	0	0	0	1	1	1	1	6
Hirakiet al.. (2017)	1	0	0	1	0	0	0	1	1	1	1	5
Emma et al.. (2018)	1	0	0	1	0	0	0	1	1	1	1	5
Ikilzeret al.. (2018)	1	0	0	1	0	0	0	1	1	1	1	5

Legend: EG - exercise group; *CG* - control group; *W* - women; *M* - men; *AT* - aerobic training; *CAPWV*- Central aortic pulse wave velocity; *HRQL* - health-related quality of life; *ET-1* - endothelin; *RT* - resistance training; *SM* - superior members; *LL* - lower limbs; *GFR* - glomerular filtration rate; *AEG* - aerobic exercise group; *CEG* - combined exercise group; *DG* - diet group; *BP* - blood pressure; *TPR* total peripheral resistance -; *TPRI* - total peripheral resistanceindex; *MAP* - mean arterial pressure; *SV* - stroke volume; *SVI* - stroke volume index; *CO* - cardiac output; *CI* - cardiac index; ↔ - there was no significance concerning Baseline; ↑ - the significant difference concerning baseline.

c) Characteristics of selected studies

In the selected articles (Table 2), the publications were from 2014[16] to 2018[17]. The sample of these studies totaled 234 individuals, where 148 were men, and 86 were women one of the selected articles used only men in its sample[18]. Three studies used men and women in their sample[16-17-19]. None of the findings used only women in their interventions. The sample sizes in the studies found ranged from 36[18] to 111 individuals[19].

The findings found in the present study, identified different protocols for the intervention, being the aerobic training [16], aerobic training combined with resistance training[17-18], and aerobic training together with caloric restriction[19]. These protocols were used to observe positive changes in the variables of body composition, muscle strength, aerobic capacity, and markers of renal function. Headley *et al..*[16] performed an aerobic training, three times a week, starting with 15 to 30 minutes, reaching up to 55 minutes (5 minutes of warm-up, 45 minutes of activity and 5 minutes of relaxation), where the patients remained between 50 to 60% of the VO_{2peak}.

Hiraki *et al..*[18] applied aerobic and resistance training, consisting of 30 minutes of walking plus strengthening of lower limbs (squat and calf lengthening) and upper limbs (strengthening of claws), with 20 to 30 repetitions, three times a week. Ikizler *et al.* [19] observed the effectiveness of aerobic training tied to a caloric restriction, where the exercise was performed for 30 to 45 minutes, three times a week, and the caloric restriction was designed to decrease calories in general. Watson *et al.* [17] performed a combined training of aerobic and resistance exercise, being 20 minutes of aerobic (thus guaranteeing the duration of the session) and 3 sets of leg press and knee extension, with the load set at 70% of 1 RM, with 12 to 15 repetitions.

One of the studies[18] took place at home, and three studies took place in laboratories, requiring the use of cycle ergometers[16-17-18]. The selected studies applied chronic interventions that were from 12 weeks[17] to 12 months 18. Regarding the responses resulting from different physical training protocols, two findings observed an increase in muscle strength[17-18], three studies verified aerobic capacity[16-17-19], two studies obtained improvement in renal function[16-18], one study investigated the oxidative stress and inflammatory response [19], one study looked at power[17], one study investigated the pulse wave velocity of the central aorta and the improvement of some aspects of health-related quality of life [16]. Below are the results of the variables identified in the studies.

Table 2: Selected studies that used physical exercise in patients with CKD.

Authors	Year	Sampling	Training protocols	DependentVariables	Results
Headley*et al..,*	2014	N= 30 women /16 men 35 a 70 years **GE:** M: 9 / H: 16 **GC:**W: 7 / H: 14	16 weeks/ 3x w./ cycle ergometer **AT** 5' warm 45' stimulus Intensity: 50-60% $VO_{2\ peak}$ 5' coll down	CAPWV Vascular Function QRVS	↔ CAPWV ↑ET-1 no EG (20,6%) ↑ aerobiccapacity aeróbica (8,3% no EG) ↑QRVS (physical functioning, vitality, and bodily pain)
Hiraki*et al..,*	2017	N= 36 men 68,7 ± 6,8 years	12 months **AT** 30' de day walking **RT** Strengthening of claws (MMSS), squat and calf enlargement (lower limbs) - 1 series, from 20 to 30 repetitions per exercise, at least 3 times a week	Muscle strength (wrist and knee extensor muscle) Alterationof renal function	↑Muscle strength ↑TGF in both groups
Ikizler*et al..,*	2018	N= 47 women /64 man 60 ± 11 years	4 months **AEG** 30'- 45'/ 3x without / treadmill, elliptical cross-training, Nu-Step cross-training and inclined exercise bike / 60 - 80% $VO_{2\ max}$	Oxidative stress and inflammation Body composition Cardiorespiratory Fitness ($VO_{2\ peak}$)	↑ oxidative stress and the inflammatory response ↔ AEG body weight ↑ body weight DG ↔ $VO_{2\ peak}$
Watson *et al..,*	2018	N= 54 **AEG**= 27	12 weeks / 3x sem. **AEG** 30' treadmill, cycling or	Muscle strength Quadriceps muscle volume	↑ Muscular strength (895 + - 408 to 1510 + - 658 kg) ↑Relative VO2 (AEG: +

	CEG= 27	rowing 70-80% of HR_{max} CEG Leg press and knee extension 3 sets 12-15 repetitions / 70% of 1RM 20 'of treadmill, cycling or rowing	Femoral rectum Cardiorespiratory fitness CardiacBioreactivity	1.1ml. Kg-1. Min-1, 5.1%, P = 0.4; GEC: + 0.6ml. Kg-1. Me-1, 2.1%, P = 0.4) ↑ Capacity↔ ↑ TPR e TPRI ↔ MAP; ↔ SV; ↔ SVI; ↔ CO e ↔ CI

Legend: EG - exercise group; *CG* - control group; *W* - women; *M* - men; *AT* – aerobic training; *CAPWV* - Central aortic pulse wave velocity; *HRQL* - health-related quality of life; *ET-1* - endothelin; *RT* - resistance training; *SM* - superior members; *LL* – lower limbs; *GFR* - glomerular filtration rate; *AEG* - aerobic exercise group; *CEG* - combined exercise group; *DG* - diet group; *BP* - blood pressure; *TPR* total peripheral resistance -; *TPRI* - total peripheral resistance index; *MAP* - mean arterial pressure; *SV* - stroke volume; *SVI* - stroke volume index; *CO* - cardiac output; *CI* - cardiac index; ↔- there was no significance concerning baseline; ↑ - the significant difference concerning baseline.

IV. Results of Measures Taken

a) Muscle strength

Hirakiet al..[18] found significant results between the exercise group (wrist: 31.7 ± 7.4 in baseline to 36.4 ± 6.4 kgf. Post-intervention; knee extensor: 0.65 ± 0.17 in baseline for 0, 70 ± 0.17 kgf. / Kg post-intervention) and the control group (wrist: 35.5 ± 8.8 to 36.5 ± 9.2 kgf. Post-intervention; knee extensor: 0.66 ± 0.15 for 0.62 ± 0.13 kgf / kg Watson et al.. 17 achieved significant results both in the aerobic exercise group and in the resistance exercise group, however, the resistance exercise group had a greater gain.

b) Aerobic capacity

The study by Headley et al..[16] observed a significant improvement in this capacity, obtaining an increase of 8.3% in the EG. Watson et al. [17] found in their study, a significant improvement in the group of combined exercises (an increase of +0.6 ml · kg-1 · min -1 2.1 %%, p = 0.04) for the group of aerobic exercises. (an increase of + 1.1 ml · kg -1 · min -1, 2.1 %%, p = 0.04).

c) Renal function

The exercise group in the study by Headley et al..[16] showed a 20.6% reduction in the ET - 1 rate. In the study by Hirakiet al.[18], renal function decreased in the GFR ratein the group that underwent intervention, from 37.0 ± 10.9 to 35.1 ± 11.4 ml/min / 1.73 m^2.

d) Oxidative stress and inflammatory response

Only the study by Ikizleret al.[19] recorded a change in these two components. Both oxidative stress and inflammatory response decreased in the control group.

e) Central aortic pulse wave velocity

Only one study by Headley et al.[16] verified this variable. There was no significant difference in both the EG and the CG, thus showing that the exercise was not effective.

V. Discussion

With the increasing incidence of CKD, with this research, we seek to verify whether the use of physical activity causes benefits in CKD patients undergoing hemodialysis treatment and what should be the best intervention method to be prescribed for this audience. A total of 43 articles were found, and of these, only 4 met our criteria [16-17-18-19]. Because of this, it is worth mentioning the presence of very few studies that investigate the effectiveness of the physical activity in patients who are in these conditions. The articles used to integrate this research obtained results in the variables offered by aerobic training [16-18-19] and resistance training associated with aerobic [17].

Regarding the study by Watson et al..[17] that verified the intervention of aerobic training with resistance training, the results obtained had great significance in muscle strength, quadriceps volume, and rectus femoris. There were also small gains in the relative VO_{2peak} and an improvement in the distance covered. Total peripheral resistance and its index increased only in the resistance training group, and blood pressure did not change. The studies by Headley et al.[16], Hirakiet al.[18] and Ikizleret al.[19], which verified only the intervention of aerobic training, had an increase in aerobic capacity, improved vasoactive balance and some aspects of health-related quality of life, increased renal function, decreased body composition (body

weight, BMI, waist-hip and the percentage of body fat), oxidative stress and inflammatory response.

The PEDro scale demonstrated that the selected studies were rated at a high level for methodological quality [15]. However, studies related to our purpose are still scarce. It is known how important physical activity is in the treatment of any organic abnormalities. Selected studies [16-17-18-19] demonstrated positive neuromuscular, cardiovascular, cardio-respiratory, biochemical, systemic responses, and quality of life aspects. However, given these results and the need for more information on the subject, more studies should be carried out to promote the reduction of knowledge gaps that still exist.

VI. Conclusion

After analyzing the studies that were used to integrate this research, we can say that the use of physical activity as a way to assist patients with CKD on hemodialysis, guarantees benefits in functional capacity, whether using aerobic training or combined training. It is worth emphasizing the need for further studies to verify which other variables may change with the use of physical activity.

Conflict of interest statement

The authors declare that there is no conflict of interest in the present study.

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Paracetamol May Increase Cardiac Congenital Malformations Risk in Prediabetic Pregnancy Women

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Abstract- Hepatic fat and abdominal adiposity in early pregnancy promotes impaired glucose homeostasis in mid-pregnancy (De Souza, 2016) and paracetamol overuse predisposes to liver fat. Hyperglycemia induces apoptosis in myocardium, and an amount evidence have demonstrated an increased risk of congenital abnormalities with gestational diabetes.

Acetaminophen overdose is the most often cause of acute liver injury and obese women are in particular risk, because is able to induce mitochondrial oxidative stress (Rousar, 2012). Acetaminophen (Paracetamol) usual high doses decreased embryonic hepatic antioxidant systems as glutathione, that play a vital role in the detoxification of exogenous and endogenous chemicals (Mitchell, 1973, Ishibashi, 1997, Beck, 2001, Rousar, 2012, rev).

The apparent safety of Paracetamol drug, a useful analgesic only (with no anti-inflammatory properties) (Neto, 2004; Hamlyn, 1978, Ucheya, 2006, Bessems, 2001) is compromized by its widespread and extensive chronic use, particularly in Peruvian population. Paracetamol though considered safe at a considerable low dose, especially in women, could cause kidney derangement and cardiac malformations during pregnant state (Ucheya, 2006), if the drug is ingested in the first trimester. Major congenital malformations, including those affecting the cardiovascular system, remain the leading cause of mortality and morbidity in infants of diabetic mothers (Pinter, 2001). Thus, there is an overcome potential maternal acetaminophen (paracetamol) toxicity (Horowitz, 1997).

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PARACETAMOLMAYINCREASECARDIACCONGENITALMALFORMATIONSRISKINPREDIABETICPREGNANCYWOMEN

Strictly as per the compliance and regulations of:

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I. Hyperglycemia and Cardiac Malformations

Prospective and retrospective cohort studies have demonstrated an increased risk of congenital abnormalities with gestational diabetes. This observation is related to the inclusion of women with unrecognized type 2 diabetes (Hoet, 1962, López-Quijada, 1974, Navarrete, 1970, Allen, 2007, Pasarella, 2013). It is known that glucose-induced malformations in animal models, including retarded growth and abnormal heart development, depend on the developmental stage of hyperglycemic exposure and glucose concentration (Roest, 2007, Scott-Drechsel, 2013).

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Diabetes mellitus in pregnancy is associated with an increased incidence of various congenital anomalies that occur during organogenesis. Pregnancy in itself is diabetogenic as a result of an augmented physiological insulin resistance (Wu, 1996; Jara, 2001). Thus, pregestational diabetes is a major risk factor of congenital heart defects (CHD).

Animal and human confirmed a role for the diabetic state and elevated insulin resistance in inducing congenital fetal malformations, and free radicals excess have been compromised by week 8 of gestation. In this way, the major congenital malformations associated with non-physiological insulin resistance in pregnancy are caudal regression and renal, cardiac and central nervous system abnormalities (Ryan, 1998, rev).

Pregestational diabetes resulted in CHDs in 58% of the offspring, including ventricular septal defect (VSD), atrial septal defect (ASD), atrioventricular septal defects (AVSD), transposition of great arteries (TGA), double outlet right ventricle (DORV) and tetralogy of Fallot (TOF). Treatment with N-acetylcysteine (NAC) in drinking water in pre-gestational diabetic mice completely eliminated the incidence of AVSD, TGA, TOF and significantly diminished the incidence of ASD and VSD (Moazzen, 2014). It has been demonstrated that maternal hyperglycemia caused a dilation of late-gestation fetal ventricular chambers, a reduction of total ventricular myocardial area, and an increase in transversal ascending thoracic aortic area (Gutierrez, 2007).

Intensive care of the pregnant mother with diabetes has dramatically decreased the incidence of diabetic embryonic malformations and clinical reports seem to link facial malformations to an increased incidence of sacral-caudal malformations in human diabetic pregnancy (Eriksson, 1985, Pinter, 1986). Indeed, congenital malformations in experimental diabetes can be prevented by antioxidants, in vivo (Simán, 1997, Reece, 1997) that replace the glutathione depletion in mother. Improving the embryonic capability to scavenge oxygen radicals, either by increasing superoxide dismutase activity or by supplying a rate-limiting precursor (N-acetylcysteine) for the enhanced synthesis of reduced glutathione, blocks the embryonic dysmorphogenesis (Wentzel, 1997).

Hyperglycemia may increase adult heart myocardial apoptosis (Gutierrez, 2009). There has been extensive evidence: maternal hyperglycemia is an inducer of birth defects that include a high incidence of cardiovascular malformations (Reece, 1997; Gutierrez, 2009).

II. Maternal Diabetes Mellitus may Cause Teratogenesis

Maternal diabetes mellitus is associated with increased teratogenesis risks, which can occur in pregestational type 1 and type 2 diabetes. Cardiac defects and neural tube defects are the most common malformations observed in fetuses of pre-gestational diabetic mothers (Corrigan, 2009). In addition, in non-diabetic populations, there is several reports that support the powerful association between maternal obesity and risk of congenital heart defects, this association was present not only for congenital heart defects as a group, but for numerous individual defects (Mills, 2010).

The significant correlation between maternal hyperglycemia in early pregnancy and the risk of fetal abnormalities in pregnant women with diabetes mellitus, particularly type 1 (Todorova, 2005) and non-known-type 2 diabetes mellitus is in line with several reports that demonstrated that fetal abnormalities are strongly associated with higher levels of glycosylated Hemoglobin in the first trimester of pregnancy. (Todorova, 2005), and this elevation in A-1c Hemoglobin has a direct correlation with hepatic glutathione levels (Sakamaki, 1999).

In this way, maternal hyperglycemia is thought to be the primary teratogen, causing particularly adverse effects on cardiovascular development. (Corrigan, 2009). Fetal cardiac defects are associated with raised maternal glycosylated hemoglobin levels up to five times more likely in infants of mothers with pre-gestational diabetes compared with those without diabetes: this cardiac defects include transposition of the great arteries, mitral and pulmonary atresia, double outlet of the right ventricle, tetralogy of Fallot, and fetal cardiomyopathy (Corrigan, 2009).

Despite improvements in prenatal care, the incidence of congenital malformations in diabetic pregnancies is still 3-4 times higher than in normal pregnancies. These defects could be attributed to alterations of intrauterine environment due to disorder of the maternal metabolism (Giavini, 1991). Glutathione (GSH), a tripeptide implicated in cellular protection against reactive oxygen species, is involved in diabetes-related embryotoxicity Interestingly, *teratogenicity of maternal serum in diabetic pregnancy is not mediated exclusively by increased concentrations of glucose and ketone bodies* as its demonstrated by Wentzel et.al (Wentzel, 1996, Wentzel, 2008). Both genetic background and obesity influence the severity of fetal abnormalities in animals (Corrigan, 2009).

Previous studies in vivo and in vitro have suggested that the oxidative metabolism of the embryo may have a role in the teratogenicity of diabetic pregnancy. In particular, the production of reactive oxygen species by the embryonic mitochondria has been implicated in the teratological process. The induction of congenital malformations by the diabetic milieu occurs during the early embryonic development (Yang, 1995). *Hyperglycemia during organogenesis has a primary deleterious effect on yolk sac function with resultant embryopathy* (Pinter, 1986).

Diabetes-induced malformations have been often related, both in vivo and in vitro studies, to morphological and physiological alterations of the yolk sac, the principal organ for the passage of nutrients from the mother to the rodent embryo (Giabini, 1993). The embryos explanted from diabetic mothers showed signs of developmental retardation and 16% were morphologically abnormal (Menegola, 1996). In addition, *reduction in embryonic GSH could reduce the protection against the oxidative stress condition described in diabetic pathology.*

Norbert Freinkel suggested that the altered fuel mixture offered to the growing conceptus may be the key to most of the changes in the embryogenesis of diabetic pregnancy. He coined the term fuel-mediated teratogénesis. In vitro (Eriksson, 1991) and in vivo, a high glucose concentration causes embryonic dysmorphogenesis by generation of free oxygen radicals. An enhanced production of such radicals in embryonic tissues is directly related to an increased risk of congenital malformations in occult diabetic pregnancy.

In this concept, an abnormal handling of reactive oxygen species (ROS) is involved in diabetes-induced dysmorphogenesis in vivo. Indeed, an increased concentration of lipid peroxides, indicating damage caused by ROS, was found in fetuses of diabetes rats. In addition, embryos of diabetic rats had low concentrations of the antioxidant vitamin E compared to control embryos (Simán, 1997 a, b). On the whole, in vivo and in vitro experiments indicate that hyperglycemia itself is not a major factor in producing diabetic embryopathies (Giavini, 1993), but several depletion of tissues glutathione does it. In this way, anti-teratogenic effects of supplementation of N-acetylcysteine in vitro has been demonstrated: N-acetylcysteine limits the teratogenicity of glucose (Wentzel, 1997, Roes, 2007).

There is a solid experimental, clinical and epidemiological evidence that support that increased glucose levels caused embryonic mal development in both normal and diabetic serum. Moreover, despite normalization of the diabetic state, the serum from the insulin-treated diabetic rats caused more growth

retardation than the nondiabetic control serum (Wentze, 1996). Therefore, the pathogenesis of fetal malformations in diabetic pregnancy is multifactorial. Thus, maintaining metabolites from all nutrient classes at a normal level may be important in preventing adverse fetal outcome (Eriksoon, 1993; Styrud, 1995)

In the second part of gestation, *the rate of heart myocardial apoptosis may increase in adult mice under a hyperglycemic environment* (Frustaci, 2000, Fiordaliso, 2001, Cai, 2002), and its observed both increased apoptosis and necrosis in myocytes, endothelial cells and fibroblasts of the human adult diabetic heart. In the fetal context, Gutierrez et al. detected ventricular chamber dilation and myocardial reduction in late gestation fetal hearts, collected from hyperglycemic pregnant CD-1 mouse dams (Gutierrez, 2007; Gutierrez, 2009).

III. Paracetamol has a Potential Teratogenic Agent

Glutathione, severely depleted in in vitro and in vivo models of diabetes (Trocino, 1995, Moazzen, 2014) is probably, the main causality factor in cardiomyocyte apoptosis (Ghosh, 2005), in addition the hyperglycemia, and both of them potentially occur, even, at usual high-doses of paracetamol.

Teratogenic potential of diabetes may consist of two components; one associated with 'direct' teratogens perturbing developmental processes in embryos at a 'critical moment' in organogenesis, and a second component, associated with a direct or indirect influence of the diabetic environment on developmental processes in the preimplantation embryos. Thus, there is a threshold glucose level associated with a clear increase of the number of litters with severely malformed fetuses in diabetics animals (Torchinsky, 1997): maternal hyperglycemia altered morphology of the late-gestation fetal mouse heart (Gutierrez, 2007).

Mitochondrial alterations produced by oxidative stress have been described in embryos developing in a diabetic environment. Interestingly, its been demonstrated recently that *Paracetamol in normal doses may be able to induce mitochondrial oxidative stress* (Rousar, 2012). In this regard, oxygen radicals-scavenging enzymes potentially reduce the embryotoxic effects induced by diabetic conditions (Menegola, 1996).

Acetaminophen overdose is the most often cause of acute liver injury. The toxic mechanism is linked to formation of an active metabolite that reacts with glutathione generating acetaminophen-glutathione conjugate (APAP-SG). This compound has been recognized to be non-toxic generally. Recent studies showed, however, that APAP-SG could possess a toxic effect too (Rousar, 2012), particularly in visceral / abdominal obese women.

Liver glutathione stores become depleted with paracetamol (Kaneo, 1994) overdoses –chronic use- so that the liver is unable to deactivate the toxic metabolites. In fact, the paracetamol induced renal damage in pregnant women results from a mechanism similar to that which is responsible for hepatotoxicity (Sule, 2006); this mechanism is probably participate in cardiac malformations in an early pregnant state.

In this context, the worldwide use of paracetamol as a household analgesic, including during pregnancy may be dangerous: in fact, fetal tissues (and maternal) can be adversely affected by paracetamol (Neto, 2004), and are potentially dangerous in the presence of chronic abdominal obesity (pathological insulin resistance) (Jara, 2001) where liver and tissues antioxidant glutathione (Reed, 1984) is reduced.

Prevention: The Exosomes in Pregnancy Cardiac Malformations

Animal models have been used to study the expression patterns of many genes that contribute to structural defects in the heart, although <10% of these underlie congenital cardiac defects in humans (Andersen, 2014, Richards, 2010, Govindsamy, 2018). Intrauterine under- or overnutrition alters offspring cardiac structure and function.

The expression of cardiac-specific genes is likely altered reflecting impaired cardiac insulin signalling that contributes to cardiac insulin resistance, that often precedes cardiovascular disease (Govindsamy, 2018), this hormonal event explains the fact that *congenital malformations occur despite good glycemic control* (Mill, 1988; Simán, 1997), thereby confirming a role for reactive oxygen species ROS and inflammatory and oxidant environment (Simán, 1997), or a lack of antioxidant protection enough, as glutathione, Vitamin E and Selenium.

Enhancing synthesis of reduced glutathione blocks the embryonic dysmorphogenesis (Wentzel, 1997), but not in cardiac malformations, because fetal heart was found to be hypertrophic (Simán, 1997) (resorption rate in fetal organs tended to be decreased with the increased dosage of vitamin E). Then, maternal administration of vitamin E can prevent congenital malformations in mid and late pregnancy, not in the early pregnancy. In comparison, Selenium may offer other additional advantages: its powerful antioxidant properties preserve reduced glutathione because its role in the major intracellular antioxidant enzyme the glutathione peroxidase (Takahashi, 1986). But Peruvian mothers don´t consume diary selenium nor vitamin D.

In addition, it is been demonstrated that acute glutathione depletion causes severe hypertension in normal rats (Vaziri, 2000): Since *Paracetamol causes physiological reduction of glutathione, we don´t surprise that this drug may increase blood pressure in advanced insulin resistant humans* (Sudano, 2010). Therefore,

pregnant women must be caution before taking this drug, but never without medical indication.

Placental cells can communicate with maternal tissues to regulate their biological function via extracellular vesicles with immune responses: the exosomes (Salomon, 2017, rev). *Acute hyperglycemia in gestation may disturb exosomes signaling (Rice, 2015), and may promotes severe malformations that occurs during organogenesis* - completed by sixth week after conception- and the critical period for malformations is almost over by the time pregnancy becomes clinically apparent. At this time, the placenta releases exosomes into the maternal circulation - Exosomes are specifically package with signaling molecules, including protein, messenger RNA, microRNA, and noncoding RNA- (Mitchell, 2015, rev), and *elevated maternal exosomes in gestational diabetes strikingly increased the risk of congenital heart defect* (Nair, 2018; Shi, 2017), and these occurs at high amounts even in pregestational maternal diabetes that induces congenital heart defects (Konečná, 2019; Zhong, 2018, rev).

Exosomes released from placental cells and adipose cells have been found to be regulated by oxygen tension and glucose concentration, and abdominal obese women release an excess of this extracellular vesicles that stimulate cytokine release from endothelial cells that increase hepatic and systemic inflammation; a lot of these events disturb placental health and fetal organogenesis in the presence of glucose intolerance exacerbate in paracetamol women consumers.

In addition ro paracetamol-side-effects at normal doses, a recent investigation has found transcriptomic changes in full-genome human miRNA expression and immune modulating effects and oxidative stress responses to paracetamol even at low doses (Jetten, 2012). Because it is very frequent that organogenesis is completed before women recognize that they are pregnant, the precounseling and strict planning of pregnancy, even in prediabetic women or gestational diabetes, become an urgent need.

IV. Conclusions

Glycolysis regulates cardiometabolism behavior during cardiac wall morphogenesis, and any disturb in metabolism pathway may alter ventricular wall morphogenesis and cause congenital cardiac malformations (Fukuda, 2019). Furthemore, *if a reduction of glutathione levels in cells has been found to increase the risks for diseases and poisoning* (Honda, 2017), *Paracetamol, is potentially dangerous in pregnant women*.

Pre-gestational maternal diabetes is associated with strong teratogenic effects on the kidney, urinary tract, and heart, and strongly associated with multiple congenital abnormalities. Pre-conception recognition of women at high risk for type 2 diabetes and optimal glycemic control may reduce the risk of congenital anomalies. A healthy diet and regular exercise (Nielsen, 2005, Allen, 2007, rev) and reduction in paracetamol-toxicity in a subclinical way, may help optimize pre-pregnancy weight and reduce the risk of congenital anomalies. Paracetamol may increase the risk of cryptorchidism and asthma during childhood as well as preeclampsia, maternal phlebothrombosis and pulmonary embolism (Burdan, 2012) as its recently reported.

In the presence of established diabetes, It is must be stress the importance of a strict metabolic control, started well before conception, to prevent excess rates of congenital malformation, and the intensive insulin therapy must be considered as an first option in this regard (Fuhrmann, 1984). Sustained hyperglycemia reduced endocardial and myocardial cell proliferation in the outflow tract of heart and lead to congenital heart malformations (Scott-Drechsel, 2013, Roest, 2006).

In diabetic women who is thinking to pregnant, an optimal metabolic control must been established (Todorova, 2005), and the danger of paracetamol use must be informed, even if the fact that most pregnancies are not recognized clinically until ≥2 weeks after conception, thus, many pregnant women are unaware of both their diabetes status during early pregnancy and the increased risk of morbidity and mortality that prediabetes or occult diabetes has on their unborn child (Roman, 2011 rev, Scott-Drechsel, 2013).

Acetaminophen (Paracetamol) is one of the most common causes of poisoning worldwide, in particular in the patients with low amount of the hepatic glutathione (Burdan, 2012, rev.), that is, insulin resistant and diabetic patients.

Abnormal Insulin Resistance in pregnancy due to excess of adipose tissue accumulation (Abdominal obesity) is associated with increased exosomes and inflammation in placental fetal unit (Jayabalan, 2017, rev): Insulin Resistance is worse with Paracetamol ingestion

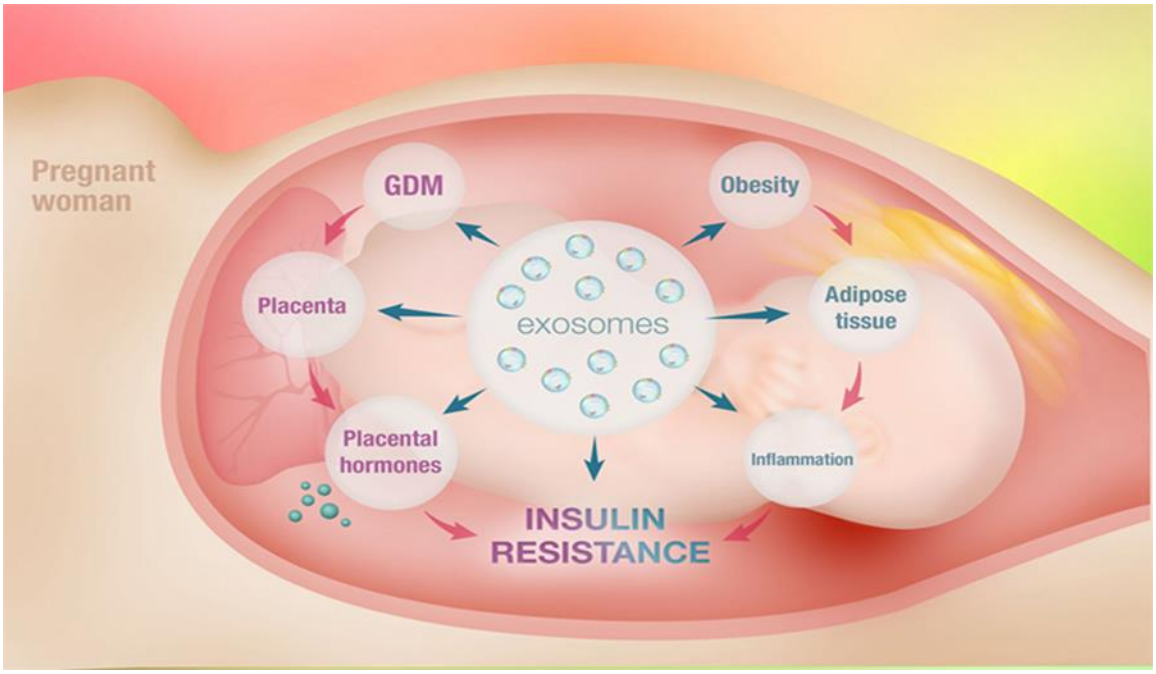

Figure 1

Paracetamol ingestion even at normal doses causes glutathione depletion in maternal liver that translate to placental and fetus, and, in gestational diabetes and pre-diabetic state induce a significant depletion in antioxidant system and cellular apoptosis in development of tissues, that promotes in the early pregnancy, cardiac malformations in offspring (Sakamaki, 1999)

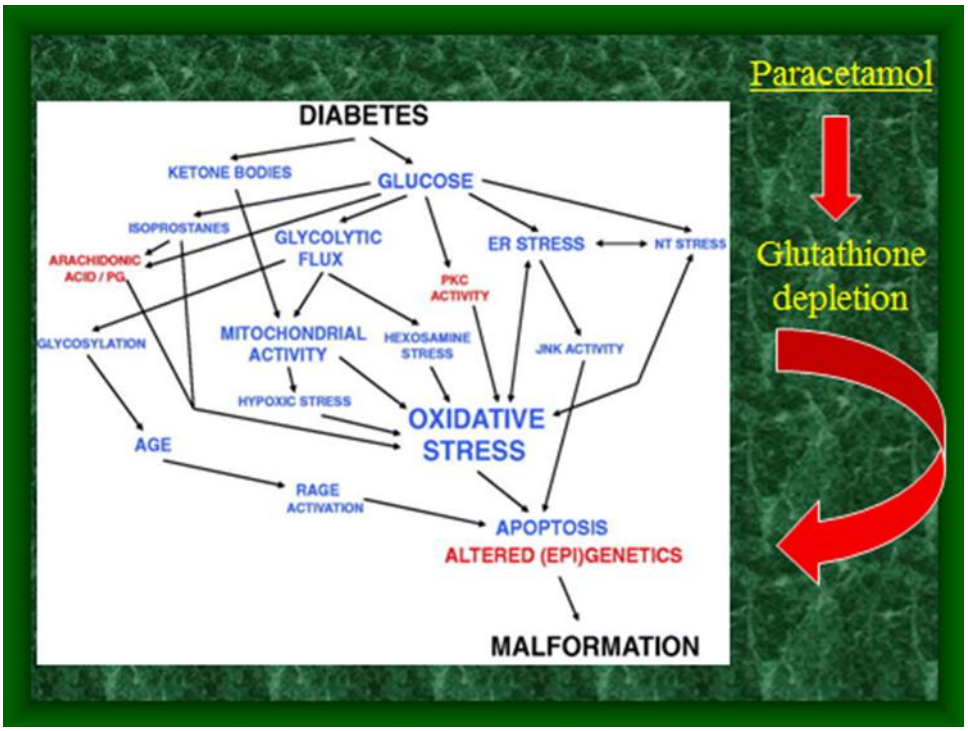

Figure 2

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Appealing Decisions

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.

Declaration of funding sources

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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.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

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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