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Gram-Positive Isolates

Implication for Re-Emergence

Highlights

Cancer and Tumor Cells

Women Patients and Household

Discovering Thoughts, Inventing Future

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Prevalence of Antimicrobial Resistance among Gram-Positive Isolates in an Adult Intensive Care Unit at a Tertiary Care Center in Saudi Arabia

By Rawan M. AlTuwaijri, Bayan T. Alzomaili, Rana S. AlZahrani, Roaa R. Amer, Samaher H. AlHarbi, AlaaAlThubaiti & Sameera M. Al Johani

King Saud Bin Abdulaziz University for Health Sciences

Abstract- *Objectives:* To estimate the prevalence of Grampositive infections in intensive care units (ICU), and to observe the patterns of resistance against different antibiotics.

Methods: A retrospective cross-sectional study was conducted of all reports of Gram-positive isolates from adult ICU of King AbdulAziz Medical City, Riyadh between 2010 and 2014. Organisms were identified and tested by an automated system and the antibiotic susceptibility was confirmed by manual method.

Results: Among 2155 Gram-positive isolates, methicillinsusceptible Staphylococcus aureus (MSSA) were the most commonly isolated organism followed by Enterococcus, Methicillin-resistant Staphylococcus aureus (MRSA), Streptococcuspneumonia andCoagulase-negative Staphylococci. MRSA resistance decreased to clindamycin, erythromycin, and trimethoprim/sulfamethoxazole. Coagulasenegative Staphylococcishowed a significant increase in the resistance to cefazolin, and erythromycin. There was an increase in resistance to ampicillin, and vancomycinamong Enterococcus, however there was a decrease in the resistance to ciprofloxacin, and nitrofurantoin. Streptococcus pneumoniae showed a significant decrease in resistance to cefotaxime (50% to 0%). Vancomycin showed 100% sensitivity to MSSA, MRSA, Coagulase negative Staphylococcus, and Streptococcus pneumoniae.

Keywords: *resistance; multidrug resistance; grampositive bacteria.*

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Conclusion: Our study revealed that antibiotic resistance among Gram-positive organisms remains a continuous issue in the healthcare setting. To reduce further progression in the emergence of MDR organisms, a continuous surveillance program for bacterial resistance is advised.

Keywords: resistance; multidrug resistance; gram-positive bacteria.

I. Introduction

During the course of management of bacterial infections, bacteria might develop the ability to resist the bactericidal or bacteriostatic effects of one or more antibiotic class (multidrug resistance (MDR)) [1]. This is usually a result of the frequent and widespread use of potent antibiotics, which is the main reason why antimicrobial resistance is more noted in the intensive care units (ICUs) in comparison to the other inpatient departments in hospitals worldwide [2]. According to the national healthcare safety network report in the United States, host risk factors for developing a nosocomial infection are age, comorbid diseases, duration of hospitalization, length of ICU stay, immune status, and disease severity. It was reported that the incidence of ICU nosocomial infections worldwide is between 5%-30% [3]. A study conducted in 8 European countries concluded that overuse was one of the factors associated with increased antibiotic resistance [4].

The patterns of antimicrobial resistance vary between ICUs in different countries due to the various factors leading to such a resistance including different patterns of infections and antibiotic use, the variations in local infection control policies, and the effective usage of the local resistance reports directing the suitable antibiotic therapies in practice, all of which will lead to different resistance patterns, and outcomes on patients and healthcare systems accordingly [5]. Over the past few years, the efficacy of antibiotics against various ICU pathogens has been decreasing, with MDRs on the rise [6]. Globally, Antibiotic resistance is still a continuous issue however due to the differences in international and national data, a local continuous surveillance studies should be conducted to identify the emergence of different bacterial resistance patterns in order to establish local guidelines. This study was done to estimate the prevalence of Gram-positive infections in intensive care units (ICU), and to observe the patterns of resistance against different antibiotics.

II. Methods

a) Study Design and Setting

A cross-sectional retrospective study was conducted on Gram-positive isolates from the adult ICU of King Abdulaziz Medical City (KAMC) between the period of 2010 and 2014. The ethics committee and

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institute review board in King Abdullah International Medical Research Centre approved this project.

b) Study Sample and Technique

The annual antibiogram data was used to calculate the percentage of resistance in Gram-positive bacteria with a total of 2155 isolates from blood, urine, sputum and respiratory aspiration. All isolates were analyzed per the guidelines of the Clinical and Laboratory Standards Institute (CLSI).The species level and AST performed using an automated system (The VITEK®2 system, BioMariex, France) to characterize all Gram-positive bacteria. All antimicrobial susceptibility testing was confirmed by manual method. Only one isolate per patient per year was used for analysis. Ampicillin, ceftazidime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, and trimethoprim-sulfamethoxazole were tested either by the breakpoint method (with the vitek 2 system) or by the ETEST method using the previously mentioned antibiotics on a Muller Hinton Agar Plate. The proportion of susceptible isolates was calculated as the sum of susceptible organisms (neither intermediately susceptible nor resistant) relative to the total number of organisms tested. Multidrug resistance was defined as resistance to three or more antimicrobials (imipenem, ceftazidime, ciprofloxacin, pipracillin-tazobactam, and/or an aminoglycoside).

c) Statistical Analysis

The trend in the resistance rate over a 5-year period (between 2010-2014) was analyzed to identify a statistically significant increasing or decreasing trend using chi-square for linear trend analysis and chi-square test was used for testing the association between categorical variables. The percent of change of antibiotic susceptibility was calculated as the difference between the later (e.g. 2014) and earlier (e.g. 2010) susceptibilities percentages divided by the earlier one. P value $<.05$ was considered as statically significant. All P values were two-tailed. SPSS software package for Windows (version 22.0, IBMCorp, Armonk, NY, USA) was used for all statistical analyses

III. Results

a) Descriptive Statistics of the Included Samples

From 2010 to 2014, there were 6611 isolated organisms in total, out of which 2155 (33%) were Gram-positive. There were 285 Gram-positive organisms isolated in 2010, 294 in 2011, 334 in 2012, 632 in 2013, and 610 in 2014. Among all isolated Gram-positive organisms, *methicillin-susceptible Staphylococcus aureus* (*MSSA*) were the most commonly isolated 849 (39%) followed by *Enterococcus* 590 (27%), *methicillin-resistant Staphylococcus aureus* (*MRSA*) 462 (21%), *Streptococcus pneumoniae* 135 (6%), *Coagulase negative Staphylococcus* 113 (5%), and *Streptococcus viridans* 6 (0.27%). All screening samples were not included to avoid false representation of colonization rather than true infection.

b) Prevalence of Antimicrobial Resistance

Over the study period, *MSSA* resistance increased to clindamycin until 2013 (5% to 12%, $p=0.15$), erythromycin (5% to 13%, $p=0.001$), and trimethoprim/sulfamethoxazole(TMP/SMX) (1% to 4%, $p=0.19$). There was no resistance to vancomycin, and penicillin throughout the study period (0%), however, from 2010 to 2013, *MSSA* was 100% resistant to moxifloxacin.

Of 590 *Enterococcus* isolates, there was an increase in ampicillin (59% to 71%, $p=0.003$), and in vancomycin resistance (37% to 46%, $p=0.170$); a decrease in the resistance to ciprofloxacin, and nitrofurantoin (96% to 76% and 66% to 54%), respectively.

MRSA resistance decreased to clindamycin (72% to 52%, $p<0.0001$), erythromycin (72% to 53%, $p<0.0001$), and TMP/SMX (60% to 46%, $p<0.0001$). However, no change was seen in *MRSA* resistance to cefazolin (1%) from 2012 to 2014, and to vancomycin (0%) throughout the study period.

Streptococcus pneumoniae showed a significant decrease in resistance to cefotaxime (50% to 0%, $p=0.003$); an increase in resistance to erythromycin (25% to 50%, $p=0.428$), and to penicillin (0% to 7%). On the other hand, there was no change in the resistance to moxifloxacin, and vancomycin (0%) throughout the study period.

Coagulase negative Staphylococcus showed significant increase in the resistance to cefazolin (54% to 90%, $p<0.0001$), and erythromycin (65% to 90%, $p=0.02$). On the other hand, *Coagulase negative Staphylococcus* resistance to TMP/SMX decreased (62% to 20%, $p=0.001$) and showed no resistant to vancomycin from 2010 to 2014.

IV. Discussion

Antimicrobial resistance is a global concern [1]. ICU is a potential source of multidrug resistance due to the widespread use of multiple antibiotics compared to other hospital departments [2]. *Methicillin sensitive Staphylococcus aureus* was found to be the most commonly isolated organism in the adult ICUs of KAMC (849 isolates). Savas et al. reported that from 597 ICU isolates, 241 were *Staphylococci*, and *MSSA* was not the most common isolates 24 (9.96%) [7]. In this study, among 1,424 *Staphylococcus isolates*, MSSA was the most commonly isolated organism 849 (59.6%). Savas et al evaluated the resistance of MSSA to clindamycin, erythromycin, and TMP/SMX, and it was 25%, 27%, and 21%, respectively [7].Looking at the ranges of MSSA resistance in this study, MSSA resistance increased to clindamycin (5% to 12%), erythromycin (5% to 13%), and

TMP/SMX (1% to 4%). In our study, vancomycin, and cefazolin remain the most effective antibiotics against *MSSA*. Comparison of the overall resistance pattern is illustrated in table-1.

Although *MRSA* is considered an endemic in many hospitals worldwide, it is still difficult to be eradicated, and remains a major concern in all ICUs [8].*MRSA* is showing a significant increase in prevalence in many ICUs reaching to 60% of all isolates [9]. In this study, from 2010 to 2014 and among 2155 Gram-positive isolates, *MRSA* were the third most common isolates in KAMC adult ICU 462 (21%).Vancomycin is considered the most important antibiotic used for *MRSA* till date [10].However, *MRSA* showed a resistance against vancomycin in other reported studies [10].Fortunately enough, throughout our study period, *MRSA* showed no resistance to vancomycin in KAMC adult ICUs. Comparison of the overall resistance pattern is illustrated in table-1.

Enterococci are considered one of the most common causes of hospital-acquired infections. In the past 20 years, *Enterococci* have become increasingly resistant to many antibiotics [9]. Recent studies conducted to assess the incidence of multidrug resistant Gram-positive pathogens showed that *Enterococcusfaecalis* accounted for 15.7% of all Gram-positive isolates. In our study, we found that 27% of all Gram-positive isolates were *Enterococcus*. Hällgren A et al. Evaluated the resistance of *Enterococcusfaecium* to ampicillin, vancomycin, and ciprofloxacin and it was 74.3%, 1.4%, and 82.4% respectively [11]. In this study the resistance pattern of *Enterococcus* to ampicillin, and ciprofloxacin was almost the same as the resistance that was reported by Hällgren A et al., 71% and 76% respectively. However, *Enterococcus* was highly resistant to vancomycin 46%. Comparison of the overall resistance pattern is illustrated in table-2.

In this study, from 2010 to 2014 and among 2155 Gram-positive isolates, *Streptococcus pneumoniae* accounted for 6%, and *Coagulase-negative Staphylococci* accounted for 5% of all Gram-positive isolates. On the other hand, in a recent study, among 1416 pathogens isolates, *Streptococcus pneumoniae* accounted for 6% and *Coagulase-negative Staphylococci* accounted for 8.3% of all isolates in the ICU with 99.1%, and 71% susceptibility to vancomycin, respectively [12]. In ourstudy, *Streptococcus pneumoniae* showed almost no resistance to ceftriaxone, moxifloxacin, andvancomycin. *Coagulase-negative Staphylococci*is 100% sensitive to vancomycin. Comparison of the overall resistance pattern is illustrated in table-2.

V. Conclusion

Our study revealed that antibiotic resistance among Gram-positive organisms remains a continuous issue in adult ICU, KAMC- Riyadh. Among all isolated Gram-positive organisms, the most commonly isolated were *MSSA* (39%), *Enterococcus* (27%), and *MRSA* (21%). Vancomycin remains the most effective drug against *MSSA, MRSA*, *Streptococcus pneumonia*, and *Coagulase-negative Staphylococci.* The overuse of multiple antibiotics in ICU is considered one of the reasons behind the significant resistance. Therefore, strict adherence to infection prevention guidelines and continuous monitoring to antimicrobial resistance are essential to avoid major outbreak in the future.

Limitation: This study was conducted in a single center in Riyadh (KAMC) and in a limited period of time 2010-2014 which could be considered as a limitation to our findings.In addition, the data was collected from the yearly antibiogram. Therefore, Patients data such as age, sex and antibiotic use were not possible to obtain to study some of the risk factors

Acknowledgment: We thank Dr. NazishMasud in helping us to review this paper

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Appendix 1: Table 1-2

Table 1: Comparison between 2010 and 2014 antibiotic resistance of *Methicillin sensitive Staphylococcus aureus*and*Methicillin-resistant Staphylococcus aureus*

Antibiotic	Resistance (%) in 2010	Resistance (%) in 2014	Trend
Methicillin sensitive Staphylococcus aureus (MSSA)			
Trimethoprim/sulfamethoxazole	1%	7%	↑
Clindamycin	5%	7%	↑
Erythromycin	5%	13%	↑
Cefazolin	2%	0%	↓
Vancomycin	0%	0%	–
Methicillin-resistant Staphylococcus aureus (MRSA)			
Trimethoprim/sulfamethoxazole	60%	46%	↓
Clindamycin	72%	52%	↓
Erythromycin	72%	53%	↓
Cefazolin	1%	1%	–
Vancomycin	0%	0%	–

Table 2: Comparison between 2010 and 2014 antibiotic resistance of *Enterococcus, Streptococcus pneumonia* and *Coagulase-negative staphylococci*

Antibiotic	Resistance (%) in 2010	Resistance (%) in 2014	Trend
Enterococcus			
Ampicillin	51%	71%	↑
Nitrofurantoin	66%	54%	↓
Vancomycin	37%	64%	↑
Streptococcus pneumonia			
Cefotaxime	50%	0%	↓
Erythromycin	25%	50%	↑
Moxifloxacin	0%	0%	–
Penicillin	0%	7%	↑
Vancomycin	0%	0%	–
Coagulase-negative Staphylococci			
Trimethoprim/sulfamethoxazole	62%	20%	↓
Clindamycin	62%	67%	↑
Erythromycin	65%	90%	↑
Vancomycin	0%	0%	–

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Anti-Cancer Activities of Cu(Ⅱ) Ion Solution in Progression and Development against Cancer and Tumor Cells

By Dr. Tsuneo Ishida

Abstract- Copper plays important role of cancer cell progression and development, malignant cell growth, and angiogenesis in invasive and metastatic growths. Specially, angiogenesis and autophagy have been worthy of new blood vessel formations and fusion proteins respectively for malignant and tumor cell growths. Schiff base copper(Ⅱ) complexes have anti-proliferative activity against cancer cells. Cu^{2+} ions play an important role as pro-cancer factor in tumor tissues especially in tumor angiogenesis, invasion, and metastasis.Specially, Cu^{2+} ions as Cu-chelating complex can inhibit formation of new blood vessel of tumor cell against angiogenesis in cancer.Promotion and development of cancer tissues have been proceeding with homeostatic imbalances of copper, in which can be caused by the uptake of excessive amounts of copper and some genetic defects.Cancer cell killing via ROS that superoxide anion O_2 $^-$, hydroxyl radical ・OH, hydrogen peroxide H_2O_2 mainly may be performed under cellular Cu^{2+} ions induced ROS generations in tumor cells. Finally, Cu^{2+}-H_2O_2 induced DNA base-pairs inhibition can be regarded as being undergone to DNA damages due to Cu^{2+}- complex formations within DNA base-pairs G≡C, A=T by Cu^{2+} substitutions in hydrogen bonds of DNA base-pairs.

Keywords: copper(Ⅰ) and copper(Ⅱ) ions, cancer and tumor cells, angiogenesis, reactive oxygen species (ROS), DNA base-pairs.

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Keywords: copper(Ⅰ) and copper(Ⅱ) ions, cancer and tumor cells, angiogenesis, reactive oxygen species (ROS), DNA base-pairs.

I. Introduction

Copper is essential trace element that has the catalysis of a wide range of enzymatic activities, including those involved in the processes of energy production such as cytochrome oxidase, the cell response to oxidant injuries of Cu-Zn superoxide dismutase(SOD). In healthy human adults, the necessity copper daily dietary intake is said to be 1～2 mg. Cu^{2+} ion is reduced to Cu^{+} and then carried into cells by various transmembrane transporters. Copper and zinc are essential for optimal innate immune function and nutritional copper deficiency leads to increased susceptibility to bacterial infection[1].In the blood, the major copper carrying proteins is ceruloplasmin[2]and the rest of copper is transported by albumin and histidine[3].Formation of new blood vessels by a tumor enable tumor growth, invasion, and metastasis facilitates easily to occur. Then, organic chelators of copper can passively reduce cellular copper and serve the role as inhibitors for angiogenesis. Depletion of copper has been shown to inhibit angiogenesis in a wide variety of cancer cell and xenograft system[4]. Anti-angiogenic strategies of blood vessel for vasculogenesis, arteriogenesis and angiogenesis are performed[4], in which are the embryological formation of new blood vessels, the remodeling of an existing artery to increase its cross-section in response to increased blood flow, and the budding of new capillary branches from existing blood vessels[4].The progenitor cells migrate to sites of vascularization and differentiate into endothelial cells, forming the vascular plexus. Especially, copper has been suggested as an important co-factor for angiogenesis[5]. It is also a major copper ion that having been found in variety of tumor tissues and are involved in tumor angiogenesis processes on copper-mediated tumor proteasome inhibition[6].Several clinical trials using copper chelation as either an adjuvant or primary therapy have been conducted.Copper can influence the major stages of tumorigenesis-initiation, promotion, progression, invasion, and metastasis. Copper ions also play a significant role for autophagy of anticancer immunity and immunogenicity,autophagy of tumor antigen, and autophagy in cancer immunotherapy based on preclinical references[7].Further, copper dependent oxidative damage can be prevented by chelation with the antioxidants dipeptides which with imidazole ring chelate copper.As cancer cells exist probably under significant oxidative stress, the cytotoxic levels could be a successful anticancer approach, in which leads to increases of reactive oxygen species(ROS)[8,9] stress and ROS (O_2^- to H_2O_2) and oxygen by generations of copper-zinc SOD enzymes[8].

On the other hand, cancer is one of the leading causes of mortality and represents a tremendous burden on patients and societies.Colorectal cancers are associated with one of the highest morbidity and mortality rates in both men and women.Cancer arises from a single cell, in which malignant tumors are described as monoclonal, meaning that each tumor arises from a single cell. Cancer cells are characterized by increased proliferation and reduced apoptosis.The development of a malignant tumor from a normal cell usually inhibitions forthe driving force in cancer progression may be various molecular such as

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proteasome[5], autophagy[7], metal-compounds[10], etc., but the underlying molecular mechanism remains unclear. Tumor microenvironment[11], K-ras mutations[12], and Haplo-insufficiency[13] as a driving force are new findings highlight to investigate cancer invasion and metastasis.Recently, it is worth noting that copper chelation[14]and Cu-polymer compounds[15] kill the cancer cells with copper-binding protein formations[16].Thus, copper is a vital mineral essential for many biological processes, in which copper also plays an important role in promoting physiological and malignant angiogenesis.Copper deficiency as an anti-cancer strategy is that in an early(phase Ⅱ) clinical trial have led to ongoing phase Ⅱ evaluation of the copper chelatorTetrathiomolybdate(TM, as an anti-angiogenic agent) in patients with advanced cancers[17]. The TM may be most beneficial for patient with minimal disease burden in the metastatic setting, in which ongoing phase studies as well as future trials will attempt to exploit this knowledge to define the role of TM in cancer treatment. The other, the vast majorityof all Cu in healthy humans is associated with enzyme prosthetic groups or bound to proteins.Excess or toxicity of Cu, which is associated with the pathogenesis of hepatic disorder, neurodegenerative changes and other disease condition, can occur when Cu homeostasis is disrupted[18].

In this review, it has becoming revealed on the standpoint of the results obtained from Cu^{2+} ion killing mechanism against bacteria whether Cu^{2+} ions and its compounds may be directly suppressed against the cancer and tumor cells.

II. Bacteriolysis of S.aureus PGN and E.coli Outer Membrane Cell Walls by Cu^{2+} Ion Solutions

Cu^{2+} ions are important as antibacterial agents for bacteriostatic and bactericide actions in bacterial cells. **Table 1** shows the bacteriostasis as disinfection agent inhibiting the bacteria growth and multiplying organism of Cu^{2+} ion, in which minimum inhibitory concentration, MIC= 50 mg/L above was obtained for Cu^{2+} ion concentration range of 0.10～50 mg/L against *E.coli*[19].**Table 2** indicates the results as bactericide action, in which MIC=625 mg/L and minimum bactericide concentration, MBC=1250 mg/L were obtained for Cu^{2+} ion concentration range of 9.8～5000 mg/L against *S.aureus*[20]. The killing curve of Cu^{2+} ions is shown in **Fig.1** (measurement's error=±6%), in which killing effects for the copper(Ⅱ) ions appear sufficiently. Killing mechanisms of Cu^{2+} ion solutions against bacteria are outlined below.①Bacteriolysis of *S.aureus* peptidoglycan(PGN) cell wall by Cu^{2+} ions is ascribed to the inhibition of PGN elongation due to the damages of PGN biosynthesis; transglycosylase (TG), transpeptidase (TP) and the activations of PGN autolysins. The other,②bacteriolysis of *E.coli* outer membrane cell wall by Cu^{2+} ions is attributed to the destruction of outer membrane structure and to the inhibition of PGN elongation due to the damage of PGN biosynthesis TP[21] and the activations of PGN autolysins[22].

Table 1: MIC measurements of Cu^{2+} commercial solution agents against *E.coli* as a bacteiostatic action by liquid medium method

Cu^{2+}solution agent· original conc 500 mg/L	Cu^{2+} solution concentration(mg/L)										MIC 50 mg/L above
	50	25	12.5	6.25	3.13	1.56	0.78	0.39	0.20	0.10	
	+	+	+	+	+	+	+	+	+	+	

(+)；Visible bacterial growth (−)；No visible bacterial growth

Table 2 : MIC, MBC, and CFU of Cu^{2+} in $Cu(NO_3)_2 3H_2O$ solution against *S.aureus* as a bactericidal action

Antibacterial agent $Cu(NO_3)_2 3H_2O$solution	Cu^{2+} concentration (mg/L)									
	5000	2500	1250	625	313	156	78	39	20	9.8
MIC	−	−	−	−	+	+	+	+	+	+
MBC	−	−	−	+	+	+	+	+	+	+
CFU(cfu/mL)	＜10	＜10	＜10	1.1×10^2	3.1×10^8	4.0×10^8	4.5×10^8	5.1×10^8	5.5×10^8	5.3×10^8

(+) ; Bacterial growth(visible turbidity), (−) ; No visible bacterial growth

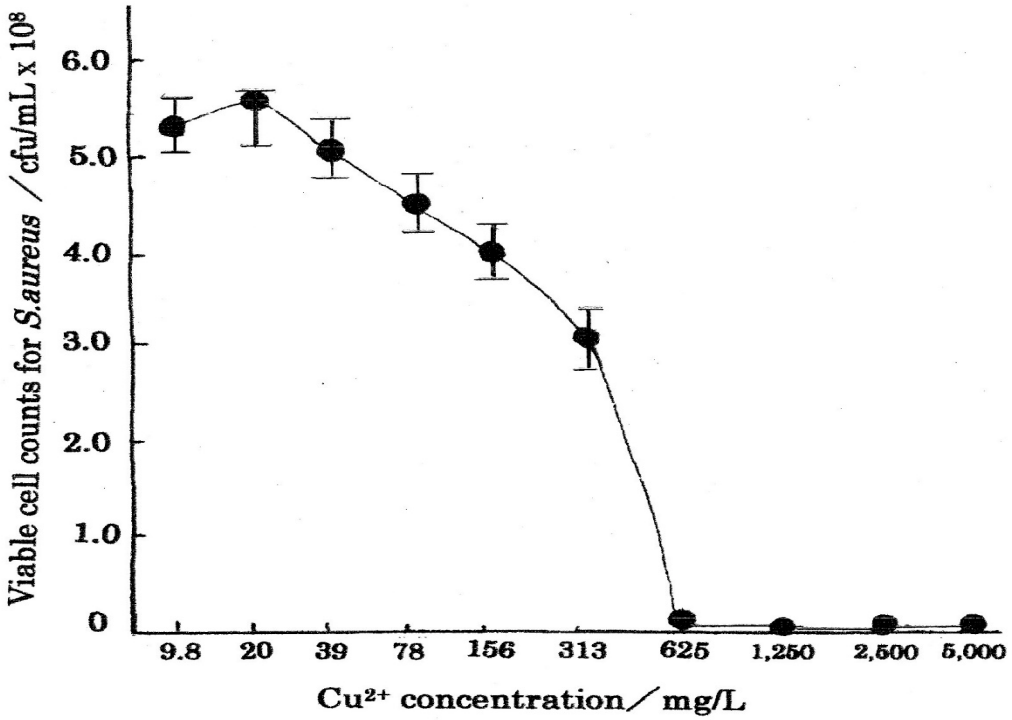

Fig. 1: Relationship between increasing Cu^{2+} concentration(mg/L) and viable counts(CFU/mL) against *S.aureus*

In the cancer and tumor cells, the killing modes are elucidated, it must be clear in this study that the inhibitions of progression and development, invasion, and metastasis of tumor cell may occur by Cu^{2+} induced autophagy fusion proteins in cancer and tumor cells.

III. Cancer Development and Progression

Cancer process is comprised of initiated cancer, development and progression of cancer, proliferation, invasion, and metastasis.Progression process of cancerous changes is considered for the cancer and tumor cells in the following:

① Abnormal cell generation ⇒ ② Formation of malignant cell and growth ⇒ ③ Proliferation and invasion ⇒ ④ Metastasis ⇒ ⑤ Dedifferentiation and stage of propagation in single cell.

Copper becomes an essential cofactor for cancer cell proliferation, differentiation, invasion, and metastasis,and apoptosis and necrosis.

Carcinogenesis follows the activation of oncogenes and the deactivation of tumor suppression genes.Apoptosis is highly regulated process of cell death in the development and maintenance of a normal cell population in mature organism. Deregulation of apoptosis pathways is thus a key feature of carcinogenesis.This chapter describes the anti-cancer activities of Cu^{2+} transfer process into initiation, promotion, malignant cell,cell invasion and metastasis against cancer and tumor cells.

a) Cancer prevention and initiated process

Clioquinol(CQ)-$CuCl_2$ mixture[23] indicates a formation of a stable CQ-Cu complex, and 1,10-phenanthroine[24] promotes copper complexes into tumor cells and induces apoptosis by inhibiting the proteasome activity. Catechins, the dietary phytochemicals present in green tea and other beverages, are considered to bepotent inducers of apoptosis and cytotoxicity to cancer cells, in which the antioxidant properties make cancer induction lowering and impeding oxidative injury to DNA[25]. The cellular DNA breakage was found to be significantly enhanced in the presence of copper ions. These Cu complexes play role of cancer prevention.

b) Promotion

Initiation process: copper(Ⅱ) ions inactivate catalyst enzyme with forming Cu^{+} ions.

$$Cu^{2+} + -SH \rightarrow -SCu(I) + H^{+}$$

Oxygen in the cell varies reductive superoxide anion, that generates hydrogen peroxide.

$$O_2 + e^{-} \rightarrow O_2^{-}$$

$$2O_2^{-} + 2H^{+} \rightarrow H_2O_2 + O_2$$

$$O_2^{-} + H_2O_2 \rightarrow OH^{-} + \cdot OH + O_2^{-}$$

$$O_2 + e^{-} + H^{+} \rightarrow \cdot HO_2$$

$$\cdot HO_2 \rightarrow H^{+} + O_2$$

Cu^{2+} ions are in turn reduced to Cu (Ⅰ) ions by superoxide anion O_2^-. The copper (Ⅰ) ions can reduce hydrogen peroxide H_2O_2 to hydroxyl radical ·OH.

$$Cu^{2+} + O_2^- \rightarrow Cu^+ + O_2$$
$$Cu^+ + H_2O_2 \rightarrow Cu^{2+} + \cdot OH + OH^-$$

c) Progression

Progression of cancer or tumor cell is considered that the uncontrolled cell growth for a carcinogenesis, oncogenesis, epigenesis[26] and the migration for intercellular ion channels[27] are focused on the identification. Epigenetics in carcinogenesis, progression, and metastasis occurring from cancer stem cell have investigated that many epigenetic changes such as hypomethylation of oncogenes, hypermethylation of tumor suppressor genes, are known to be associated with many cancers. The other, the intracellular ion channels have emerged as oncogenic proteins, since they have an aberrant expression in cancers compared to normal tissues and contribute to several hallmarks of cancer. Carcinogenesis follows the activation of oncogenes and the deactivation of tumor suppression genes.

Cu^{2+} induced initial cancer cell ROS production and oxidative stress against tumor cell[28].

In free radicals (O_2^-, H^+, OH^-,·OH) and H_2O_2 are formed as follows[29]:

$$\cdot O_2^- + 2H^+ + e^- \rightarrow H_2O_2$$
$$H_2O_2 + e^- \rightarrow HO^- + \cdot OH$$
$$\cdot OH + e^- + H^+ \rightarrow H_2O$$
$$2H^+ + \cdot O_2^- + \cdot O_2^- \rightarrow H_2O_2 + O_2$$
$$H_2O \rightarrow \cdot OH + \cdot H + e^- \rightarrow H_2O_2$$

In the cell wall, reacting with polyunsaturated fatty acids(L=Organic ligand).:

$$LH + OH\cdot \rightarrow L\cdot + HOH$$
$$L\cdot + O_2 \rightarrow LOO\cdot$$
$$LH + LOO\cdot \rightarrow L\cdot + LOOH$$

Reactive oxygen species (ROS) $O_2^-$and H_2O_2 generated in cell wall permeate into cell membrane and cytoplasm, in which in cell membrane high reactive ·OH and OH^- are formed by Haber-Weiss and Fenton reactions.

Haber-Weiss reaction[30]; $H_2O_2 + O_2^- \rightarrow \cdot OH + OH^- + O_2$

Fenton reaction[31]; $Cu^+ + H_2O_2 \rightarrow \cdot OH + OH^- + Cu^{2+}$

Furthermore, new ROS productions occur by Fenton-like type. L=Ligand

$$LCu(Ⅱ) + H_2O_2 \rightarrow LCu(Ⅰ) + \cdot OOH + H^+$$
$$LCu(Ⅰ) + H_2O_2 \rightarrow LCu(Ⅱ) + \cdot OH + OH^-$$

The other, relation of oxidative stress and autophagy has been investigated for copper ion in Cu_2O, CuO crystals. The aqueous systems as following reaction[32]:

$$Cu_2O + 2H^+ \rightarrow 2Cu^+ + H_2O$$

and

$$CuO + 2H^+ \rightarrow Cu^{2+} + H_2O$$

Cu^+ ion is unstable and easily oxidized to Cu^{2+} ion in aqueous system by Fenton reaction. Hence, in blood it is not proper as Cu^+ ion rapidly is oxidized to Cu^{2+} ion. However, although "self-eating" by autophagy can potentially lead to cell death when cytoplasmic cellular organelles are consumed beyond a critical-for-cell-survival point, it is unclear whether autophagy represent an active dying mode or the cell desperate, and often exhausted, attempt to survive.

d) Invasion and metastasis

Cancer cell invasion has collective and individual cell migrations, by which cancer cells invade other tissues either by moving collectively as epithelial sheets or detached cluster, or as single cells via mesenchymal or amoeboid cell types[33]. During cancer progression, a variety of tumor cells show changes in their plasticity by morphological and phenotypical conversions, including the epithelial to mesenchymal transition (EMT). EMT has been increasingly recognized as crucial events in cancer progression and metastasis. Human epithelial cells predominantly migrate collectively, while most cells observed in vivo using intravital techniques and in vitro studies migrate as single cells[34].

The other, metastasis is a multi-step process encompassing, ① the local infiltration of tumor cells into the adjacent tissue, ② transendothelial migration of cancer cells into vessels known as intravasation, ③ survival in the circulatory system, ④ extravasation and ⑤ subsequently, proliferation in competent organs leading to colonization[35]. The rate-determining step process is that there is great interest in understanding the regulation of cellular adhesion metal-protein molecule. The epithelial to mesenchymal transition (EMT) is observed phenomenon that is a vital aspect of embryogenesis as well as cancer progression. During the EMT, cancer cells lose their adhesion and begin the process of metastasis ①. The process of cancer cell transition from EMT plays a dominant role in facilitating metastasis and progression in many types of cancer. Cuprous oxide nanoparticle (CONPs) induce mitochondria-mediated apoptosis, indicating that can inhibit the growth and metastasis of cancer cells[36].

IV. Cu^{2+} ions Induced the Activations of Cu Binding, Autophagy, Copper Chelation, DNA Damages, and Killing in Cancer and Tumor Cells

a) Cu^{2+} ions binding with amino, peptide, protein of cancer cell tissues

Cu^{2+} ions inhibit polymerization of glycan chains, to be thought to be forming copper complex in

which is partial action sites of glycan saccharide chains. L is coordinated molecular.

$$Cu^{2+} + LH \rightarrow CuL^{+} + H^{+}$$
$$CuL^{+} + LH \rightarrow CuL_2 + H^{+}$$
$$Cu^{2+} + 2LH \rightarrow CuL_2 + H^{+}$$

Peptide copper complex may be formed as 3N-Cu-O, $Cu(Gly\text{-}L\text{-}Ala)H_2O$. Specially,$Cu^{2+}$ ions react with such as cross linked molecular penta glycine$(Gly)_5$, copper-glycine complex may be formed.

Amino acid : $Cu^{2+} + Gly^{-} \rightarrow Cu(Gly)^{+}$, $Cu(Gly)^{+} + Gly^{-} \rightarrow Cu(Gly)_2$,

Peptido : $Cu^{2+} + GlyGly \rightarrow Cu(GlyGly)$, $Cu(GlyGly) + Gly^{-} \rightarrow Cu(GlyGlyGly)^{-}$.

b) Autophagy in cancer cell

Autophagy plays an important role in cancer and tumor cells. However, how autophagy contributes to cancer ontogenesis and progression has turned out to be more complex than expected. It must be clear whether Cu^{2+} ions induced autophagy or necrotic cell death. Autophagy is to be function as tumor suppression of damaged organelles/proteins, and to confer stress tolerance that can maintain tumor cell, and to be a mechanism of cell death. MCF-7 cells influenced with tested Cu(Ⅱ) complexes produced LC3 protein after 72 hours incubation indicating autophagy in MCF-7 cancer cells[37]. Further, the specific nanomedicine induced phage fusion protein in cancer cell occur, that has shown significant improvements in the therapeutic activity of currently existing drug delivery system, such as liposomal doxorubicin. Thus, this fact is implicated that in the cancer and tumor cells, the killing modes are elucidated, it must be clear in this study that the inhibitions of progression and development, invasion, and metastasis of tumor cell occur by Cu^{2+} induced autophagy fusion proteins in cancer and tumor cells[38]. Furthermore, autophagic anticancer immunity pays attention in which autophagy affects the anti-cancer immune response. Accumulated studies have demonstrated that triggering autophagy is able to facilitate anticancer immunity due to an increase in immunogenicity, whereas other studies suggested that autophagy is likely to disarm anticancer immunity mediated by nature killer(NK) cell.Cu_2O crystals promote endothelial cell death via Cu^{+} induced autophagy, and elevate the level of reactive oxygen species such as superoxide and nitric oxide[36].Active role of autophagy as a cell death mechanism can be in principle validated by experiments documenting prolongation of survival upon autography downregulation[36]. However, the endothelial cell death by Cu^{+} ion induced autophagy is unclear whether the tumor death is due to fusion proteins in process of autophagy[38].

c) Cu^{2+} ions, copper complexes and copper-chelating suppress tumor development and angiogenesis in the cancer cell

Tumors are to grow and thrive that they must develop a blood supply. Thus, it is said that every increment in tumor growth requires an increment in capillary growth, in which neovascularization or mechanism by that tumor cells elicit new blood vessel growth from the surrounding tissue. Angiogenesis is a complex process with many different growth factor and inhibited by a diverse range of proteins. The molecules secreted by tumors act on stromal cells in a paracrine fashion, so that can have different activities with the production and secretion of antiangiogenic proteins. Copper is required for high levels of angiogenesis, in which copper requirement is due to many angiogenic factors. Angiogenesis relies on the coordination with many different activities in copper complex and copper-chelating for suppressor tumor.

Copper as a neovascular agent is required for angiogenesis, in which micro-molar amounts of Cu(10^{-6} M), thus appeared to control endothelial cell migration and angiogenesis. Copper was shown to stimulate blood vessel formation in the avascular cornea of rabbits, only recently have clinical trials established that Cu privation by diet or by Cu chelators diminishes a tumor's ability to mount an angiogenic response[39].Nanoparticles of copper(NanoCu) stimulate angiogenesis at molecular level[40]. NanoCu affect the development of blood vessel and muscles in a different manner than Cu salts, in which have pro-angiogenic properties at the systemic level, to a greater degree than $CuSO_4$ salt. The other, NanoCu also were confirmed that demonstrating significant effects on mRNA concentration and on mRNA gene expression of all pro-angiogenic and pro-proliferative genes measured.

Tetrathiomolybdate(MoS_4^{2-},TM)[41] is a very promising antiangiogenic agent, and a potent metal chelator that binds Cu to proteins such as serum albumin, forming a complex that is only sparingly taken up by cells. The underlying concept for TM efficacy as an anticancer agent is that when the copper status is in the window, cellular copper needs are met and toxicity is avoided. Copper deficiency induced TM[42], depletion of copper[43]and copper-lowering[44] were significantly impaired tumor growth and angiogenesis, encouraging results in canine study of advanced and metastatic cancer. Further, the copper-chelating agents are efficient for Trientine Dihydrochloride (trientine), suppressor tumor development and angiogenesis[10].

d) Copper-nucleotide interaction and Cu^{2+}-DNA: Cu^{2+} substitution to hydrogen bond in DNA base pairs

Cu^{2+} ion induced occurrence of generations of ROS and hydrogen peroxide H_2O_2 in tumor cells damages DNA in tumor, in which formation of DNA

damage resulting from a release of catalytic copper and binding of copper to DNA with generation of ·OH radicals, and by reaction of H_2O_2 with the metal produces the strand breaks in DNA as well as DNA base modifications and deoxyribose fragmentation.

It has been found that in aqueous solution coordination of Cu^{2+} to the N7 and N1 sites of purine rings is pH dependent and coordination to N7 diminishes as pH of the solution increases[8]. The sites of action tending to bind purine base A(adenine), G(guanine) and pyrimidine base C(cytosine), T(thymine) of nucleic acid bases for individual metals are indicated[45], depending on acid dissociation constant pK_a. According to the theory, it is shown in Fig.2, that is represented to substituting of Cu^{2+} ions into hydrogen bonds in DNA base-pairing G≡C and A=T pairs. Thus, it may be considered that DNA damages due to copper complexes formation within DNA base-pairs G≡C, A=Toccur in cytoplasm of cancer cell.

e) Copper complexes induced the killing, the regulation, the suppressor against cancer and tumor cells

Copper compounds, complexes, and chelation act beneficial for specific malignant tumors. The anticancer activity of Cu(Ⅱ) depending disulfiram(DS) is high against cancer cell of metastatic liver cancer, prostate cancer that supplementing with Cu, DS is highly toxic to cancer cell[46,47]. Anticancer activity is exhibited by copper(Ⅰ) complex possessing pyridine-type ligands(pyridine, bipyridine, phenanthroline etc.) or such where copper(Ⅰ) ion is coordinated to phosphine ligands.

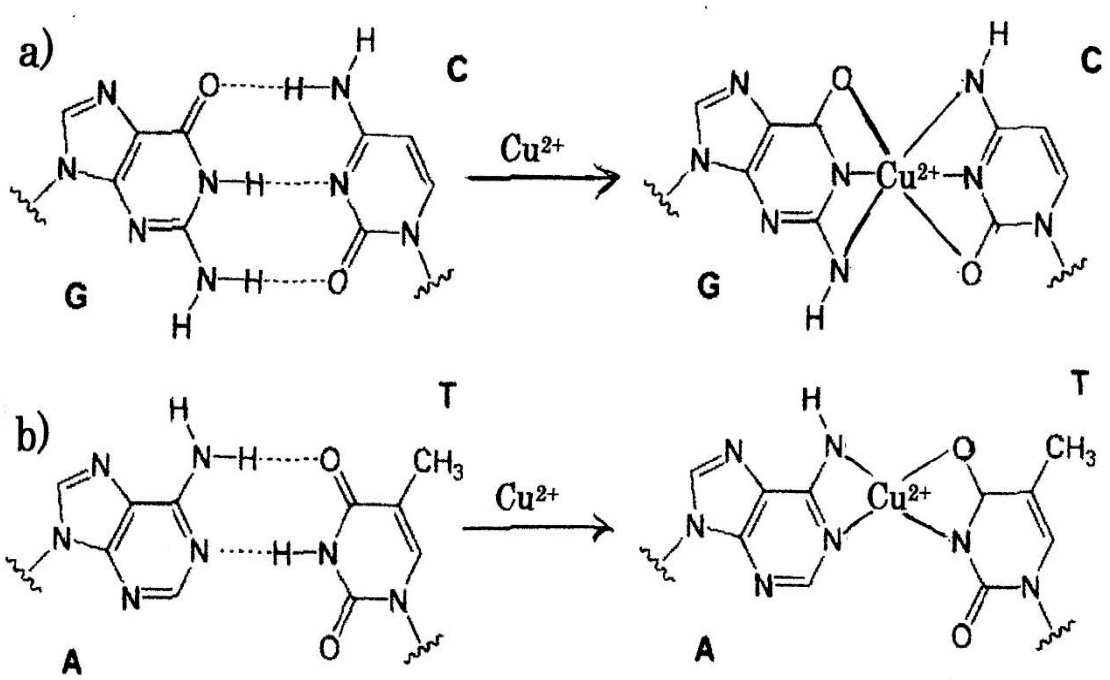

Fig. 2: Cu^{2+} substitution into the triple and double hydrogen bonds in DNA base-pairing G:C, A:T pairs
a) G≡C base pair, regular octahedron, 6-coodinated structure, Cu complex formation(stable)
b) A=T base pair, planar square, 4-coodinated structure, Cu complex formation(unstable)

These both types of ligands to one molecule would make it possible to create a compound with an increased activity against cancer cells[48]. The novel Cu(Ⅱ) compound with a binucleating ligand containing a phenol scaffold and two triazza crown binding sites that is occurring within DNA cleavage on cancer cell growth and induces apoptotic cell death of Capan-1 pancreatic cancer cells[49]. Also, the anticancer action of Casiopeinas, copper coordinated complexes of Cu(N-N)(A-A)NO_3, (A-A=N-O,O-O)) with perceptible antineoplastic effects on human malignant glioma had been investigated[50,51,52]. The result is that the CasiopeniaⅢ-ia significantly inhibited cell proliferation and cell death, inducing autophagy and apoptosis of glioma cells, which correlated with the formation of autophagic vacuoles, over expression of Bax and Bid proteins. New uses for old copper binding drugs[53] is approached to discover new application for a specific cancer cell death inducer, including pro-angiogenic process.

Table 3: Anti-cancer activities of Cu^{2+} ions for the initiation, progression, proliferation, invasion and metastasis against cancer and tumor cells

Cu^{2+} ion solution	Progression and Growth of Cancer and Tumor Cells				
	Prevention Carcinogenesis	**Promotion** Tumorigenesis-initiation,	**Progression** Oncogenes Malignant cell formation	**Proliferation and Invasion** Angiogenesis Invasive growth Cell migration	**Metastasis** Angiogenesis Transendothelial migration
Cu^{2+}	**Cu^{2+}** ・Clioquinol(CQ)-$CuCl_2$ mixture ・1,10-phenanthroine ・Catechins-Cu^{2+} ・Autophagy for cancer prevention (Cu_2O crystal)	**Cu^{+}, Cu^{2+}** **O_2^-, H_2O_2** ・ROS and SOD ・Initial tumor formation and growth **・Cu^{2+} + -SH →** **-SCu(Ⅰ) + H+** **・O_2 + e → O_2^-** **・$2O_2^-$ + $2H^+$ →** **H_2O_2 + O_2**	**Cu^{+}, Cu^{2+}** **O_2^-,・OH, H_2O_2** **OOH^-** ・Tumor progression ・Haber-Weiss reaction: **$H_2O_2 + O_2^- \rightarrow$** **・OH+$OH^-$+$O_2$** ・Fenton reaction: **$Cu^+ + H_2O_2 \rightarrow$** **・OH +OH+$Cu^{2+}$** $LCu(Ⅱ) + H_2O_2$ →$LCu(Ⅰ)$ + ・OOH + H^+ $LCu(Ⅰ) + H_2O_2$ → $LCu(Ⅱ)$+ ・OH + OH^-	**Cu^{2+}** **O_2^-,・OH,H_2O_2** **・Anti-angiogenesis** ・Autophagy and fusion protein ・Cu lowering with proteasome ・DNA damages ・ROS generation to inhibit tumor cell growth **・Cu-mediated proteasome for inhibition of proliferation and cell death** ・Malignant cell killing via ROS	**Cu^{2+}** **・OH, H_2O_2** **Anti-angiogenesis** ・Inhibitor of angiogenesis ・Anti-metastatic effects: EMT-Cu^{2+} ・Anti-metastasis by Cu_2O**(Cu^+)** ・Suppression of tumor growth by Cu depletion **・Nano Cu, Cu-chelation,and Cu-complexes induced necrotic cell death**

Furthermore, the copper chelation kills the cancer and tumor cells, in which an alternative Cu-chelators[10] and TPEN-copper complex using a cyclic amino metal chelator[54]could inhibit and suppress neovascularization, increase of apoptosis in tumor growth, and angiogenesis. Copper chelating complex can serve as anti-angiogenic agent and ROS generators to inhibit tumor growth. Killing of cancer cell is induced via ROS mainly consisting of singlet oxygen, O_2^-,・OH,and H_2O_2.

As the summary of above-mentioned results, Table 3 represents the anti-cancer activities for Cu^{2+} ions migration into initiation, progression, proliferation, invasion, and metastasis against cancer and tumor cells.

V. Conclusions

Cu^{2+}ions have numerous roles in cancer prevention, initiation of carcinogenesis, progression of uncontrolled cell growth, malignant tumor cell growth, invasive growth as malignancy, and metastasis of down-regulation of cell adhesion and cell-cell attachment, by Cu(Ⅰ)/Cu(Ⅱ) redox reaction cycles and Cu^{2+} ion induced ROS productions.Angiogenesis and autophagy play an important role in cancer and tumor cells. Schiff base copper(Ⅱ) complexes have anti-proliferative activity against cancer cells. Cu^{2+} ions play an important role as pro-cancer factor in tumor tissues, especially in tumor angiogenesis,invasion, and metastasis. Cu^{2+} ions as Cu-chelating complex can inhibit formation of new blood vessel of tumor cell against angiogenesis in cancer.Promotion and development of cancer tissues have been proceeding with homeostatic imbalances of copper, in which can be caused by the uptake of excessive amounts of copper and some genetic defects.Cancer cell killing via ROS that superoxide anion O_2^-, hydroxyl radical ·OH, hydrogen peroxide H_2O_2mainly may be performed under cellular Cu^{2+} ions induced ROS generations in tumor cells. Finally, Cu^{2+}-H_2O_2 induced DNA base-pairs inhibition can be regarded as being undergone to DNA damages due to Cu^{2+}-complex formations within DNA base-pairs G≡C, A=T by Cu^{2+}substitutions in hydrogen bonds of DNA base-pairs.

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Pain Syndrome Removing at Patients with Temporomandibular Joint Disorders and Urinary System

By O. Volovar, V. Malanchuk, O. Kryzhanivska & N. Lytovchenko

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Abstract- Actuality of using the nonsteroidal anti-inflammatory drugs for complex temporomandibular joint (TMJ) degenerative-dystrophic disorders treatment acquiring further more significance due to increasing of this widespread pathology among the different gender and age of person.

Offered results of using the selective cyclooxygenase (COX-2) inhibitors drug-orodispersible form of Meloxicam for patient with TMJ osteoarthritis and urinary diseases.

Decreasing of the TMJ pain syndrome either during chewing or calm state, jaws activity volume was improved, crackling and crepitation at the joint were decreased.

Effectiveness and safety of using the orodispersible tablets of Meloxicam for treatment of TMJ osteoarthritis were estimated.

Keywords: meloxicam, temporomandibular joint, osteoarthritis, urinary diseases.

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Pain Syndrome Removing at Patients with Temporomandibular Joint Disorders and Urinary System

O. Volovar [α], V. Malanchuk [α], O. Kryzhanivska [σ] & N. Lytovchenko [ρ]

Abstract- **Actuality of using the nonsteroidal anti-inflammatory drugs for complex temporomandibular joint (TMJ) degenerative-dystrophic disorders treatment_acquiring further more significance due to increasing of this widespread pathology among the different gender and age of person.**

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I. Introduction

Diseases of the temporomandibular joint (TMJ) are one of the most common problems of dentistry, maxillofacial surgery. In recent years, a lot of work has been devoted to this subject, which focused on the widespread prevalence of TMJ diseases in people of different sex and age, and the difficulties of their treatment (19, 27, 31). Degenerative-dystrophic TMJ diseases often occurs in patients with undifferentiated connective tissue dysplasia (CT) based on the background of a variety of concomitant somatic diseases, including the urinary system deseases (up to 49%) (28).

Osteoarthrosis (OA) is a chronic degenerative-dystrophic joint disease, based on the degeneration of articular cartilage, which leads to its thinning and a decrease in the amount of cartilaginous tissue, structural changes and exposure of the subchondral bone and the formation of bone enlargements. OA TMJ is a multifactorial disease, factors such as age and genetic predisposition, abnormalities or disruption of the functioning of the joint and surrounding muscles, trauma of the joints or mandible, congenital weakness (CT) of the organism, endocrine diseases, metabolic disorders, autoimmune diseases, etc. (19, 28).

OA TMJ is often accompanied by pain, resulting in limited activity, and often in disability, and decreased quality of life of patients (14, 24).

In the basis of OA there is an imbalance between the anabolic and catabolic processes in the joint tissues, especially in the hyalin cartilage, where the main pathological changes occur. The main sign of OA is the degeneration of articular (hyaline) cartilage, namely, the inadequate synthesis of chondrocytes of proteoglycans (PG) and the fragmentation of proteoglycan aggregates, which are the most important components of pathological disorders in this disease (26).

Despite the fact that OA is not usually referred to as inflammatory arthropathy, but is considered as a degenerative joint disease, more and more evidence has recently emerged that suggest that inflammation plays a key role in the progression of this degenerative disease (11, 15, 30).

The result of chronic persistent inflammation in the tissues of the joint and synovitis is the degradation of articular cartilage and remodeling of the subchondral plate of the bone. In this case, the cartilage is thinned, narrowing the articular crack and forming osteophytes and subhondral cysts. In addition, there is a damage of other tissues of the joint, in particular, the synovial membrane, the articular capsule, intra-articular ligaments, and articular muscles. The leading clinical symptoms of OA TMJ are joint pain, limitation of its functions, and articular sounds (26, 31).

The main complaint of the patients with OA TMJ who consult dental surgeon with OA TMJ is pain. The innervation of tissues and facial organs is wide. There is a corresponding area in the cerebral cortex. Patients characterize pain as moderate or severe irradiation, or permanent pain, which increases during movements of the mandible (15, 19, 20, 29).

In the treatment of OA TMJ the clinical picture, the stage of the disease and pain should be taken into account. Treatment is aimed at inhibition of activity of the inflammatory process, prevention of joint degradation, restoration of its function, etc. (19, 30).

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According to the recommendations of the European Antireumatic League (EULAR), the pharmacological treatment of OA TMJ includes systemic and topical application of nonsteroidal anti-inflammatory drugs (NSAIDs) – selective and nonselective cyclooxygenase-2 inhibitors (COX-2), as well as slow-acting chondroprotective drugs (SYSADOA-symptomatic slow acting drugs of osteoarthritis: glucosamine sulfate, chondroitin sulfate, diacerein, avocados / soy noncommunicable compounds), intraarticular injections of corticosteroids and cartilage biopolymers (12, 32).

One of the universal groups of drugs are NSAIDs. These drugs occupy a central place in the treatment of pain syndrome in OA TMJ and combine anti-inflammatory, antipyretic, analgesic and antithrombotic properties. NSAIDs reduce the inflammatory process, although most of them (salicylates, ibuprofen, naproxen, tiaprofenic acid) suppress the metabolism of hyaline cartilage, which contribute to the progression of OA (5, 21, 24).

The advantage of selective COX-2 inhibitors is their stimulating effect on cartilage tissue anabolism by inhibiting the expression of IL 1 and its receptor. These drugs help accelerate the synthesis of growth factors, including the transforming growth factor β and insulin-like growth factor, inhibit Aggrecan degradation, inhibit cartilage catabolism, neutralize the effect of MMP and reduce the intensity of apoptosis of chondrocytes. Drugs of this group disrupt the synthesis of prostaglandins, reduce the sensitivity of pain receptors to bradykinin, reduce swelling of tissues in the inflammation center, weaken the mechanical compression of nociceptors (1, 7, 18).

Meloxicam is a selective COX-2 inhibitor, which has a high anti-inflammatory, analgesic and antipyretic activity. It is a derivative of enolic acid, belongs to the class of oxycamines. Due to its selectivity with regard to COX-2 isoenzymes, it has a high gastrointestinal safety profile compared to other drugs of this group (1, 22). Compared to other NSAIDs, Meloxicam does not increase the risk of developing heart attack (myocardial infarction), heart failure, arterial hypertension and liver failure (21).

A significant group of negative NSAID reactions is a malfunction of renal blood flow and nephrotoxicity, which appears in the form of fluid retention, hypernatremia, increased serum creatinine levels, and high blood pressure. NSAIDs can induce the development of interstitial nephritis. According to a number of researchers, NSAIDs are the launch of existing conditions that contribute to kidney damage, such as hypertension, chronic pain that is often observed in chronic renal dysfunction (2). On the background of the use of selective COX-2 inhibitors, in particular, Meloxicam, there was no significant increase in the risk of renal insufficiency and its progression in patients with moderate renal insufficiency (clearance of creatinine – 20-40 ml/min) (8).

Biological effects of Meloxicam: suppresses the expression of COX-1 and to a greater extent COX-2; suppresses the synthesis of prostaglandins; suppresses the synthesis of leukotrienes; has an anabolic effect; suppresses IL 1β, IL 6, FNP α; suppresses IL-1-mediated production of metalloproteinases (MMP); affects transcription factors, mainly on NF κB; suppresses the release of lysosomal enzymes; suppresses the production of NO in chondrocytes in both healthy and having OA people (individuals); affects free radicals; inhibits proliferation of synoviocytes; dose-dependent stimulates the synthesis of PG and hyaluronic acid (HA); stimulates the synthesis of glycosaminoglycans in cartilage; suppresses the agrikan's degradation; neutralizes the effect of MMP; inhibits apoptosis of chondrocytes (1, 23, 25).

The pharmacokinetics of Meloxicam: the drug has 99% bind with plasma proteins (mainly albumin), permeability in synovial fluid is 50% compared to plasma, metabolized in the liver almost completely with the formation of four pharmacologically inactive derivatives. Elimination of Meloxicam is mainly in the form of metabolites in equal parts with feces (less than 5%) and urine (small amount). The half-life is 15-20 hours, plasma clearance is an average of 8 ml / min.

Contraindications for the prescription of Meloxicam are: hypersensitivity to Meloxicam or other components of the drug, as well as to active substances with a similar effect, such as acetylsalicylic acid; gastrointestinal bleeding or perforated gastric or duodenal ulcer in the anamnesis; severe hepatic or renal failure; blood coagulation system failure; severe heart failure; treatment of perioperative pain in coronary bypass surgery.

Meloxicam has shown high efficiency and good tolerability in both during intramuscular injections and at oral intake, including patients with OA TMJ with high cardiovascular and gastrointestinal risks (9, 24).

In cases when oral administration of drugs in the form of tablets or capsules is difficult for the patient NSAIDs are used in the form of soluble powders (sachets), syrups, orodispersible tablets (ODT) that are dissolved in the oral cavity during a short time (10-30 seconds). Due to this, the amount of the drug subjected to presystemic metabolism or the effect of primary passage through the gastrointestinal tract (GIT) and the liver (4) decreases (compared to a standard solid pill).

Advantages of ODT: convenience of application; the possibility of taking the drug in case when rapid effect is needed; increased bioavailability; the possibility of prescription to elderly patients, as well as other groups of patients who are having difficulty with traditional oral medicine; elimination the risk of strangulation or spasm; improving the perception of the

drug in all groups of patients thanks to its pleasant taste (8, 9).

NSAIDs with OA can be used locally, in the form of ointments and gels, and is usually prescribed before oral application of NSAIDs, or in combination with it. The use of NSAIDs locally gives a good clinical effect with a much lower frequency of side effects from the digestive system, but it cannot be compared to the effectiveness of oral forms. To achieve maximum clinical effect, it is recommended to apply ointment locally together with oral forms of NSAIDs (24, 27).

II. Purpose of the Work

Evaluate the efficacy and safety of Meloxicam in the form of ODT in patients with degenerative-dystrophic TMJ diseases with the background of concomitant urinary tract pathology.

III. Materials and Methods

The study involved 38 patients (11 men and 27 women) with OA TMJ, an average age of 45.3 ± 7.6, in which there was a history of concomitant pathology of the urinary system, no allergic reactions to NSAIDs, coagulation of blood, gastrointestinal bleeding or perforation of the stomach; no severe cardiac, hepatic or renal failure. Patients were treated at the Dental Medical Center of the Bogomolets National Medical University and the Department of Nephrology and Hemodialysis of Kyiv City Clinical Hospital № 3.

Patients were divided into 2 groups: the main group – 19 people, comparative group – 19 people.

The examination of patients was carried out according to the classic method of examination of patients with TMJ diseases. In the course of this the following were determined: patient's complaints, the cause and duration of the disease, the peculiarities of its course, the presence of concomitant pathology. The objective examination took into account the degree of mouth opening, the volume of movements of the mandible, displacement of the jaw when opening the mouth in one direction or another. Auscultatory the presence of sounds (noises) in the joint was noted. Palpation of TMJ was performed, the presence or absence of pain in the joint and masticatory muscles (temporal, i.e. masseter, pterygoid) was diagnosed.

The severity of the pain was evaluated on the Verbal Descriptor Scale (VDS) scale, according to which: 0 points – no pain, 2 points – weak pain, 4 points – moderate pain, 6 points – severe pain, 8 points – very severe pain, 10 points – unbearable pain (6, 13).

Additional methods of the study were orthopantomography with the study of the shape of the mandibular heads, X-ray of the opened mouth by the Parma, MRI of the TMJ. Since patients had a history of an existing concomitant pathology of the urinary system, a nephrologist consultation with ultrasound examination of the kidneys and urinary tract, and urine tests was mandatory.

Anti-inflammatory non-steroidal drugs were being receiving by the patients in for 7 days (main group: Meloxicam in the form of ODT 15 mg / day; comparative group: Nimesulide – 200 mg daily), chondroprotectors for 2-3 months (Chondroitin sulfate and Glucosamine hydrochloride - 1000 mg daily), combined calcium supplements for 2-3 months (calcium-D3 Nicomed - 2 tablets daily, Calcemin-advance - 2 tablets daily). A thin layer of ointment with anti-inflammatory and warming effect was applied locally 2-3- times a day on the area of TMJ and masticatory muscles. An ointment contained methyl salicylate, camphor, thymol, terpentine and eucalyptus oil. Patients were observed at 7, 21, 30 days of treatment.

IV. Results

Among all patients with TMJ diseases included in this study, the nosology of the diseases of the concomitant pathology of the urinary system was as follows: crystalluria (oxalate or urat) – 9 (23.7 ± 3.1), nephroptosis – 8 (21.1 ± 2, 8%), chronic pyelonephritis – 6 (15,8 ± 1,9%), urolithiasis – 5 (10,5 ± 1,2%), chronic cystitis - 5 (10,5 ± 1,2%), L-shaped kidney – 2 (5.3 ± 0.5%), pyelectasia – 2 (5.3 ± 0.5%), bladder prolapse – 1 (0.5 ± 0.4).

The majority of patients – 33 (86.8%) complained of pain in the TMJ. A moderate dull pain at rest was observed in 21 (55.3%) patients according to VDS of 3.47 ± 1.11 points. In these patients, during chewing on solid food or active motions of the mandible, the pain intensified and was 6.09 ± 1.33 points of VDS. Less than half of patients – 12 (31.6%) complained of severe TMJ pain only when they opened the mouth and chewed on solid food, which was 6.11 ± 1.22 points of VDS, and no pain was observed at rest.

The duration of the disease from 1 month to 1 year was observed in 15 (39.5%) examined, from 1 to 5 years in 23 (60.5%) patients. In 25 (65.8%) patients, X-ray signs of osteoarthritis of the TMJ had been diagnosed, which corresponded to the 1st or 2nd degree of the disease according to the N.N. Kasparov (1981), respectively 16 (42.1%) and 9 (23.7%) patients. The X-ray revealed uneven, indistinct contours of the mandibular heads, changes in their shape, thinning of the cortical layer, narrowed and uneven articular gap. MRI of the TMJ results showed thinning of the cartilage of the mandibular head and its destruction was observed in 3 (7.9%) persons.

Constraint in the affected joint area was observed in 21 (55.3%) patients, which usually continued from 15 to 20 minutes in the morning, and gradually decreased and disappeared. When opening

the mouth, 100% of patients noted the appearance of crepitation or rash in the joint.

During the examination of patients, the restriction of the jaw movements was experienced, in which the opening of the mouth was 3.25 ± 0.86 cm. While opening the mouth, the jaw shift was diagnosed towards to the affected TMJ, crunching or crepitation in the joint, moderate pain when pressed on the chin that took place on the pathological side and according to the VDS was 4.84 ± 1.0 points. Palpation of TMJ and masticatory muscles in most patients was painless – 23 (60.5%) patients. In 15 (39.5%) men, trigger points were observed in the anterior parts of the temporal, lower external areas of the masseter muscle, medial pterygoid muscle in the place of its attachment to the inner surface of the mandible. A crunching was noted at vertical, sagittal, transversal movements in the affected joint. Mostly, patients had one-sided lesion of the TMJ.

During a 100% main group study, one week after treatment, it was found that TMJ pain tends to disappear in 10-15 minutes after receiving 1 ODT of Meloxicam 15 mg, which was 2.76 ± 0.93 of VDS. After 15-25 minutes, the patients observed almost complete reduction of pain at rest – 1.58 ± 1.07 points. During chewing, pain remained but became less intense (3.26 ± 0.99 points): in 12 (63.2%) patients the pain was moderate, and 7 (36.8%) patients had mild pain. The duration of anesthetic effect was observed within 1 day; patients did not require re-administration of NSAIDs.

In patients of comparing group on the 7th day of treatment, it was found that pain in the TMJ decreased after 20-30 minutes (2.93 ± 1.01 points) after taking 100 mg of Nimesulide, and a significant decrease (1.47 ± 0.9 points) was marked by patients in 50-60 minutes. The pain during chewing and opening the mouth after an hour was also less intense (3.37 ± 1.16 points) and patients were able to take food without significant discomfort. The duration of the analgesic effect of Nimesulide was observed within 10-12 hours, after which the pain in the TMJ began to increase and patients were forced to re-take the drug.

During repeated visits an increase in the opening of the mouth to 4,02 ± 0,95 cm was noted in patients of both groups, as well as the volume of jaw movements improved, crunching and crepitation in the joint decreased.

In patients of comparison group after 7 days of treatment, most patients noted discomfort in the epigastric area, and 5 people also noted heartburn in the stomach. These patients were prescribed gastro protectors (decoction of flax, Bi_2O 120 mg twice a day). On the 5th day of taking of the Nimesulide 2 patients noted aching pain and heaviness in the lumbar area. After the examination and urinalysis modification detection (the appearance of protein to 0.33 g/l and unmodified erythrocytes in sight) it was recommended by the nephrologist to discontinue the drug.

In the main group, Meloxicam in the form of ODT was well tolerated by patients, had no irritating effect on the mucous membrane of the gastrointestinal tract, urinary tract, no allergic reactions. Patients noticed that ODT was pleasing to taste, quickly dispersed in the oral cavity. The pain decreased in 20 minutes and did not occur for a long time, which did not require re-administration of NSAIDs during the day. The control of urine tests did not reveal any changes in relation to the initial level. In addition to this, patients indicated a decrease in emotional stress, fear of limiting movements of the mandible, improvement of the general condition of patients.

V. Conclusions

The pain in the TMJ at rest, as well as when opening the mouth and chewing decreased at patients with degenerative-dystrophic diseases of TMJ and concomitant pathology of the urinary tract system during taking Meloxicam in the form of ODT 15 mg daily. The volume of the movements of the mandible improved, the opening of the mouth was 4.02 ± 0.95 cm, crunch and crepitation in the joint decreased.

The drug has an evident pain relief effect that comes quickly and lasting for a long time. ODT Meloxicam is well tolerated by patients, has a pleasant berry flavor, is convenient in use, has no undesirable effects on the digestive tract and urinary system and side effects. The psycho-emotional state of patients was normalized.

Meloxicam ODT can be used in patients to eliminate the pain syndrome in the complex treatment of patients with degenerative-dystrophic TMJ diseases, compared to the receiving of Nimesulide does not cause irritation from the digestive and urinary system.

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Type II Diabetes in Mauritius: A Qualitative Investigation into Women Patients and Household Support during Pregnancy

By Beebeejaun-Muslum Zareen Nishaat

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Abstract- The global burden of non-communicable diseases (NCD's) is escalating, principally due to a sharp rise in developing countries experiences of rapid economic transitions from subsistence and agricultural based economies to more technology based economies that are characteristic of sedentary based employment. Lifestyle changes in Mauritius too, with a population of barely 1.3 million inhabitants, have resulted in dramatic increases in the incidence of Type 11diabetes. Diabetes mellitus is a condition in which the body's capacity to utilise glucose, fat and protein is disturbed due to insulin deficiency or insulin resistance. The epidemic is chiefly type II diabetes which along with genetic susceptibility, particularly in certain ethnic groups such as Asians, is brought on by environmental and behavioural factors. Gestational Type 2 Diabetes (GDM) is defined as carbohydrate intolerance that begins or is first recognised during pregnancy. During pregnancy, the women is objectified, feeling a loss of control and an awareness of having an unwell, high risk body. Findings showed that pregnant women with GDM this study as extremely vulnerable. Behaviours of health professionals, such as nurses, midwives and physicians and of relatives, friends and employers influenced the women. An open caring relationship where the individual women is understood and supported, empowered to strive for normal glycaemia, and encouraged to be reconciled with her disease. It also includes informing her partner and other significant persons about her need for support.

Keywords: type II diabetes, women patients, household support, pregnancy.

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Type II Diabetes in Mauritius: A Qualitative Investigation into Women Patients and Household Support during Pregnancy

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Abstract- The global burden of non-communicable diseases (NCD's) is escalating, principally due to a sharp rise in developing countries experiences of rapid economic transitions from subsistence and agricultural based economies to more technology based economies that are characteristic of sedentary based employment. Lifestyle changes in Mauritius too, with a population of barely 1.3 million inhabitants, have resulted in dramatic increases in the incidence of Type 11diabetes. Diabetes mellitus is a condition in which the body's capacity to utilise glucose, fat and protein is disturbed due to insulin deficiency or insulin resistance. The epidemic is chiefly type II diabetes which along with genetic susceptibility, particularly in certain ethnic groups such as Asians, is brought on by environmental and behavioural factors. Gestational Type 2 Diabetes (GDM) is defined as carbohydrate intolerance that begins or is first recognised during pregnancy. During pregnancy, the women is objectified, feeling a loss of control and an awareness of having an unwell, high risk body. Findings showed that pregnant women with GDM this study as extremely vulnerable. Behaviours of health professionals, such as nurses, midwives and physicians and of relatives, friends and employers influenced the women. An open caring relationship where the individual women is understood and supported, empowered to strive for normal glycaemia, and encouraged to be reconciled with her disease. It also includes informing her partner and other significant persons about her need for support.

Keywords: type II diabetes, women patients, household support, pregnancy.

I. Introduction

Mauritius is an island situated in the Indian Ocean, with a population of 1.15 million made up of five different ethnic groups: Indian, Creole, Muslim, Chinese and European. World Health Organisation (WHO) reports indicate that Mauritius has one of the highest of non-insulin dependent diabetes in the world. There are a variety of contributing factors for this, some of which include genetic predisposition, rapid change in eating habits (e.g. influx of fast foods) due to rapid industrialization, obesity and lack of exercise.

In the population group of 25 years and over, 12.7% (52,000 individuals) have diabetes and a further 17.5% (83,000 individuals) have impaired glucose tolerance, whereas in the population group of 45 years and over, 23% (42,000) have diabetes and a further 22% (40,000 individuals) have impaired glucose tolerance (CSO Mauritius Survey,2017).

Over the past 2 decades, the prevalence of diabetes in Mauritius has remained one of the highest in the world with no recent significant improvement. Mauritius ranked 2nd in 2002 and 4th in the world in 2009 with nearly one in five of its adult population above the age of 30 years being affected. Nearly half of those affected do not know that they have the disease and this adversely influences quality of life, risks of complications as well as morbidity and mortality.

Despite the availability of free health services, over 50% of diabetes patients are poorly controlled and the risk of complications from diabetes such as cardiovascular diseases, renal failure, blindness, peripheral vascular and neurological diseases leading to lower limb amputations, remain very high. Despite continued efforts from the Ministry of Health and Quality of Life (MOH & QOL) to provide easily accessible diabetes care to all patients, the outcome remains poor. Most of the outpatients and primary health care centres are overcrowded and the set-up does not provide optimal care and attention.

II. The Mauritian Family in Context

Before industrialisation, Mauritian women either worked in agricultural fields and/or were engaged in the domestic sphere by assuming responsibility their husbands and children. With the advent of industrialisation and the establishment of the Export Processing Zone (EPZ) greater numbers of women began increasing their levels of education and engaging in more modernised-sedentary types of employment. Over the years, women have emerged from home makers to nation builders and the factors which have promoted labour force participation of women are fertility reduction, increased life expectancy, free education, economic hardships, availability of jobs and wider aspirations beyond the confines of the family and the home. Today women in Mauritius prefer to pursue a career of their own rather than spending long hours of their lives bearing and rearing children. In the pre-industrial era, predominantly agriculture the Mauritian

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family was a unit of production whereby the husband, wife and children worked as a team with other members of their extended families. But there is a major shift away from this conventional household structure, which is still evolving from the traditional extended type to a nuclear structure and nucleated families have become child centred where children are given more importance.

Gestational Type 2 Diabetes (GDM) is defined as carbohydrate intolerance that begins or is first recognised during pregnancy (Simmons, 1995). Women with an early diagnosis of GDM in the first half of pregnancy, represent a high risk subgroup with an increased incidence of obstetric complications, recurrent GDM in subsequent pregnancies and future development of diabetes. Other factors that also trigger GDM is obesity and hypertensive disorders in pregnancy. Thus, improving sensibility with diet, exercise and drugs like metformin may reduce risk of diabetes in individuals at high risk of GDM. The latter is an established risk factor for adverse maternal outcomes such as preeclampsia[1] and future T2DM, as well as neonatal outcomes such as macrosomia, hypoglycaemia and birth injuries (Wendland et al 2011, p. 11-92).

Since the purpose was to explain the understanding and perception of Diabetes that is mainly GDM, in-depth interview method was chosen. The participant for the pilot study consisted of an individual (patient) who was seven months pregnant. Only one participant was utilised because the findings revealed enough about the incidents (experiences) and support in a patient's life to warrant the interview guide and conduct further interviews. The data is not part of the work reported here.

The 40 semi-structured interviews were varied in length and were about two to three hours long. In order to directly address the research questions, this study sampled those individuals who were information rich, specifically criterion sampling. This involves "reviewing and studying all cases that meet some reviewing predetermined criterion of importance" (Patton, 2002 p. 238). The criterion for this study was that their participants had to be pregnant around six to eight months and had already been diagnosed with GDM. Almost all the interviews were conducted in the hospitals/health clinics at a time convenient for the respondents. For most of them, this was when they came for their usual check-up or for medication.

III. Medical Conditions and Support

During pregnancy, the women is objectified, feeling a loss of control and an awareness of having an unwell, high risk body (Bhat et *al*, 2010:91). The pregnant women with GDM also expresses exaggerated responsibility including constant worry, pressure and self-blame. In order to provide quality care with perinatal support, increased knowledge about life conditions for women with Type II Diabetes Mellitus (T2DM) is required.

With increasing prevalence of diabetes, the occurrence of diabetes-complicated pregnancies is also increasing. Ruggerio et *al* (1990:442) noted that compliance with medical conditions is especially important for women with gestational diabetes because of the health implications for both the mother and the foetus. The women's struggle to achieve normal blood glucose levels continued no matter under which circumstance, including severe morning sickness or separation from the child's father (Chen et al, 2012:232). The ambivalence was present among respondents when the strict lifestyle in terms of diet mainly, became 'too much' or did not result in satisfactory glucose levels. As Aneeta, a respondent who was interviewed on the 17th November 2016 described it:

"A feeling that this is an unsurmountable situation in checking my blood sugar. How can I cope with thinking about everything I eat?"

The findings showed that the women expressed a need to explain their ambivalence as respondent Sherine, interviewed on the 2nd December 2016 stated when talking about her midwife:

"She (the midwife) explained what happed in my body etc…., but very little about me as a person, what happens in my head."

Information provided by care providers could contribute to and increase worry. For instance, a nurse told Naz, a respondent interviewed on the 12th November 2016 that:

"A large baby is not a strong baby, it's a large and fragile baby."

Women who suffer from gestational diabetes often deliver large babies. One specialist diabetic nurse working in a Southern hospital exaggerated conceptions of how dangerous hyperglycaemia during labour could be for the baby. Emphasis on the increased risks had created feelings of guilt in some women. Shiroze, a respondent interviewed on 20th November 2016 expressed her feelings of guilt towards her health and her baby:

"I think in my 6th month, my HbA1C levels would not get down to at least 5.5. And the way they kept talking about that there was very, very, very, major focus on having to lower my levels because it's very dangerous for the baby"

The women felt prioritised by the care providers during pregnancy compared to ordinary diabetes care, both in terms of access, competence and attention. Professional support entailed an established, trustful and reliable relationship. One respondent who attended

[1] A condition that pregnant women develop. It is marked by high blood pressure and a high level of protein in the urine

both a public hospital and a private clinic appreciated being treated as a mother-to-be in need of specific diabetes-related competence. The increased attention from care providers at the hospital was experienced as related to the baby in the womb, its health was given highest priority and the mother's health. The latter often feels depressed and suffers from anxiety since she keeps worrying about the health of the unborn child.

"And then that's how it felt, is it just because I am carrying a baby, because otherwise they don't care, or they don't care about me. And it's very like, here you are, you are pregnant and we are focusing on the baby!"

The respondents noted a generally high level of competence concerning diabetes among the care providers but some had also experienced insufficient professional competence, including either incorrect management or no management at all. Respondent Anjalee expressed,

"This seemed to increase the feeling of pressure. Faulty to receiving answers to my questions, lead me to act on my own."

Some respondents mentioned the fact that the hospital staff were not very welcoming. They displayed harsh comments on the patients and would not bother to answer their questions. They found this attitude unpleasant and felt even more discouraged to be hospitalised. Respondent Zoya stated,

"I have never missed home as I did when I was hospitalised. I was treated merely like an object who had to be medicated and fed. In fact not only me but the other patients in the same ward felt same."

One respondent had drawn the conclusion that there were no guidelines on treatment of pregnant women with diabetes and another one, Deepika, interviewed on the 11th November 2016, had this feeling in connection with hospital treatment of a diabetes-related complication. She was hospitalised for three days was told by the charged nurse,

"She told me to take my iron tablets with a glass of juice and I told her I can't do that. She went out and checked my glucose levels which was a bit low. She repeated to take some juice and I said I can't do that because my glucose will go over the top. And then she said, Oh, yes, right!"

The respondents reported that they are constantly worried about the child and its health, however at some point in time, some of them expressed hope. Kaneez, a respondent interviewed on the 5th December 2016, expecting her third child noted:

"I know that I can have healthy children despite having diabetes. I know that I can influence it."

Despite this hopeful attitude among some respondents, or perhaps for a comforting mind, a feeling of doubt was more or less simultaneously present. As respondent Pooja said:

"I read a lot about GDM on the internet, it is often mentioned that something could go wrong for somebody and that somebody will be probably me!"

The respondents expressed a feeling of being different and outsiders. This feeling was fortified when comparing the experiences with that of pregnant, non-diabetic women. Deepika noted:

"During my hospital stay, my friends in the same ward could not understand the reason behind pregnant women with GDM going for controls early morning. Being pregnant without diabetes is nothing. Friends complaining about being pregnant without diabetes just don't understand what problems are!"

Respondent Hemlata, interviewed on the 19th December 2016 stated:

"I had no idea how it would be now that I have been tested GDM positive, how difficult or easy it would be"

Yuna, another respondent interviewed on the 14th of December 2016, was overloaded with work demands needed a certificate from her physician on order to confirm her need for 'normal' working conditions with the necessary breaks. For others, taking sick leave from work was the only solution.

During pregnancy, especially at the beginning, a women's body behaves in a different and more incomprehensible manner. Blood glucose values may be unexplainable and may rapidly decrease or increase to uncontrollable values. Some women maintained a lack of understanding including body reactions during the whole course. Jasmine was a respondent who was interviewed on the 26th of November and works as a receptionist. She noted:

"It makes no difference what one eats because the blood glucose level seems to have a life on its own anyway!"

Jasmine here means that the blood glucose level during pregnancy is so un-predictory that it seems to work by itself. However, for most women, their body's reactions gradually became increasingly more comprehensible. Housna, interviewed on the 20th of November 2016, expressed her satisfaction about testing her glucose levels several times a day and can easily decide what type of food is best for her to consume:

"I have learned so much about my body that I should have known much earlier. Now, I know quite a lot about differences in the response of blood sugar to different foods."

Dreams and plans for the child's arrival were rare or absent on several of the women's descriptions. Their decision not to rejoice made it easier to manage the birth of an unhealthy child. As Shima, a respondent

who was interviewed on the 22nd of December 2016 noted:

"I cannot dare to be happy in advance, not before everything is seen to be okay, but only when the baby is born and you can see that it is a healthy baby."

Meera, a respondent interviewed on the 14th November 2016, said that she never dared to rejoice and 'feel pregnant'. She was not used to expressing her deep feelings for others, not even her partner and she was filled with both great worry ad great loneliness. She declared:

"Mentally I have hardly known that I am pregnant. I never really 'entered' into pregnancy like other women do. It was only and mainly blood sugar. Even though I feel it kicks a bit and I can see it on the ultrasound monitor, I find it difficult to think and rejoice about it."

Many respondents expressed both the need to be responsible for their situation and a need to surrender the responsibility to health professionals. As Bani, interviewed on the 12th November 2016 stated:

"I control the disease. Being able to measure my blood sugar after every meal is a benefit. It gives me control. I feel now I am in complete control of the disease. What would it have been otherwise?"

In order to obtain all the important goal of giving birth to a healthy child, the woman needed the care of health professionals skilled in diabetes and childrearing. The health's professional knowledge, continuous information, coaching and sensitivity in relation to each women and her needs formed the basis for the women's service of control.

The struggle for optimal blood glucose levels has led to serious hypoglycaemic symptoms for some women, one respondent suffered unconsciousness with seizures and had required help from the ambulance to attain sufficient oxygen levels, while another participant, Deena felt a strong fear of dying:

"And sometimes in the evening I was like… whether I dare go to bed or not, what if I die in my sleep and my husband doesn't notice anything? That really gives you a lot of anxiety, you don't know how you are going to survive."

Care organisation during pregnancy differed in the way that no universal routine exists. The number of visits including to different specialists, increased as pregnancy proceeded. This was particularly difficult for respondents who were on sick leave, or who lived far from the care providers. They also expressed the need to share experiences with other pregnant women with diabetes. Some expressed feelings of loneliness as pregnant diabetics. Women were less satisfied with support provided by care providers with limited experience of and knowledge gaps concerning diabetic pregnancies. To be in transition to motherhood requires a supportive environment, particularly when a mother-to-be is at high risk.

Pregnant women with diabetes are at high risk of complications and are at increased risk of adverse childbirth outcomes, such as foetal congenital abnormalities, obstetrical and neonatal complications (Beckerman, 1985:82). There is a strong relationship between good glycaemic control beginning with planning pregnancy and throughout delivery and labour. Pregnant women at high risk, as in the case of diabetes feel more anxiety, worry and ambivalence than those with low-risk pregnancies (Reiss, 1992:70). However, research on how women with diabetes perceive support received during pregnancy is limited.

IV. The Supportive Role of the Family

Family ties are the foundations of the whole society and should be accorded a primacy over all others. Family obligations refer to the thought that members of the family are obliged to offer assistance to other members, having a sense of duty towards them. Assistance given in the past to genealogical kin was mostly based upon mutual self-interest rather than a sense of obligation to family members (Walker and Best, 2010:75)).

Industrialisation and urbanisation since the nineteenth century had induced radical transformation of household structures and familial responsibilities. Captured within the process of modernisation, families and households witnessed a rise in individualism, which was a significant departure of co-responsibilities but now an important pillar of modern day capitalism. These changes rearranged conventional institutions to points of irreversible social transformation, of which the "family" and "extended households" had fallen victim. Individualism gave rise to nuclear families, comprising of married couples and their biological off springs.Hencemodern society is now made up of various types of social institutions which has now widely replaced the supportive roles once played by families. For instance, with the worldwide emergence of nurseries for baby and infant care, nuclear families now have ways of breaking their reliance upon extended kinship networks.

Social networks, which are the web of social ties that surrounds an individual and social support are seen as two distinct concepts. Social support may be seen as the emotional, instrumental, financial aid that is obtained from one's social network. Support is generally considered as an exchange or transaction between people. As per House's (1981) typology, there are four types of support namely emotional, instrumental, informational and appraisal support. Emotional support means providing care, love and trust to the individual while instrumental support involves providing triangle aid to a person to complete tasks. Giving an individual

advice, suggestions and information required to tackle a problem is what is known as informational support and appraisal support consists of giving constructive feedback on one's performance which might be useful in self-evaluation (Thanacody et *al*, 2009:69).

Some studies suggest that instrumental support has a greater influence on well-being (Schultz and Parker, 2002:58) whereas others found emotional support to be most important and it has received till now the greatest impact on the recipient of support. House's typology of support is stated here because it encompasses the complexity of social support networks regarding the family. Moreover, this typology is not limited to a list of types of support, but includes dimensions underlying the different types of social support. Social support here is defined as information leading to believe that one is cared and loved, esteemed and a member of a network of mutual obligations. The evidence that supportive interactions among people in crisis from a wide variety of pathological states. It may reduce the amount of medication required, accelerate recovery and facilitate compliance with prescribed medical regimens (Dabney and Gosschalk, 2010: 71).

'Pregnancy is not just hard on the back but it is hard on the soul. Stress and anxiety, ups and downs often come together.' said one respondent, Kirtee, expecting her second child was interviewed on the 14th November 2016. She stated that she finds it very difficult to manage her household duties, elder son and her job during this pregnancy as she is experiencing more complications as compared to her first pregnancy.

More than 70% of all pregnant women experience nausea and vomiting during pregnancy and most of them report that these early pregnancy symptoms cause them to change their daily activities. O'Brian and Naber (1992:65) found that women report changes in family, social or occupational functioning as a result of first trimester symptoms. Nausea and vomiting can impose substantial lifestyle limitations on pregnant women that can have short and long term consequences for them and their families. Women reported that recumbent rest or dietary alterations provided relief.

Respondents argued the need for support in cooking. The first trimester of pregnancy is usually accompanied by vomiting and nausea which prevents the woman from even entering the kitchen. The very smell of food makes them nauseous. Respondent Shaina, interviewed on the 19th November 2016narrated that she has to cook every day for her husband and her two kids,

"Every morning I had to prepare for lunch and dinner. Every five minutes interval I felt the need to vomit. This is very unpleasant and finally I do not even want to see the food!"

Caregivers should recognise and validate the need for pregnant women to make changes in lifestyle that will enable them to achieve comfort. A longitudinal study was conducted to investigate the changes in the division of household labour and emotional support and practical support received by new mothers during first post-partum (first year after delivery) year. Women assumed primary responsibility for the majority of household tasks studied and they perceived declines over time in their husband's participation in household chores. Women's satisfaction with their husband's contribution was significantly related to their own mental health, delivery type (caesarean section), job status (bring at home job-related documents vs back at work) and husband's participation in child care and certain household chores (house cleaning, grocery, shopping, cooking, washing clothes and dishes, household repairs, car maintenance and garbage removal. Overall these findings showed diminishing levels of emotional and practical support for women at a time when the need for support was greater.

V. Spousal Support

In Mauritius where the people are mainly of Indian origin, and where life was largely of the agrarian cum indentured labour type in the nineteenth and early twentieth centuries, family structures were largely of the extended or joint patterns. Significant changes to the social fabric in Mauritius began taking place in the latter part of the twentieth century. There is a considerable variation in people's experiences of support among kin. Much of this depends upon their living arrangements, class backgrounds and inter-personal relationships. Against this varied social tapestry it would therefore be pertinent to ask: "Does people's experiences vary in relation to their social and economic positions"? A major issue here is how reliable is support between kin. There is a sense in which family relationships are regarded as providing structures of support, which are reliable but not everyone, for a range of reasons, is able to draw upon such support. The concept of exchange has often been used to describe support in families and this can be an expression of mutual self-interest. Emotional and moral support in the family comprises of mostly talking, giving advice and helping others in trying to make them feel better in their lives.

In many developing societies, family relationships remain vital as units of mutual economic and emotional support (Aruna and Reddy, 2001). Throughout the world, the value placed on the emotional quality of marital bonds is increasing. For instance, Brown et *al*, (2002:34) argued that in India, a husband's relationship to his mother is seen as traditionally more important than his relationship with his wife. Ultimately, communication and support between spouses were limited. However, there is now a reverse trend among

urban middle-class couples, Indian husbands and wives now engage in much more sustained interaction and develop close interpersonal ties in India. This type of behaviour is very common in Mauritius where a large section of the population follow the Asiatic culture. Sons are brought up like little 'kings' in many households and when they get married they expect the same treatment from their wives.

As Anjalee said,

"You see, what is worst here is that my husband, despite having an illegal relationship, had support from his parents. I was blamed not to be attractive enough (... you know... sexy and appealing...) and that's why he had an affair!"

The sexual division of domestic tasks at home has somewhat weakened as the employment of wives and mothers has increased. Nevertheless, in most families, the wife still carries the major responsibility for housework. It has been found that gender integration of paid work increases husband's participation in domestic work, which contributes to wife's marital happiness. Many respondents related that benefitting emotional support from their husband leaves them happy and this strengthens their relationship. As Rachelle pointed out,

"When the doctor diagnosed me with gestational diabetes, my husband was very worried and immediately asked about the procedures to follow, like diet and medications. He takes care of me very well and does my shopping for diabetic food."

Another respondent Deepika, interviewed on the 12th of November 2016, appreciated her husband's determination in helping her maintaining a good no sugar diet. She said:

"I was amazingly surprised to see my husband on the same diet as me! He said that this is also his part sacrifice to have a healthy baby. Since I am enduring so much pain and health complications, he can do this small effort for me."

The implications of numerous types of support varies with the changing needs of women as they move from pregnancy to labour. During pregnancy, emotional and tangible support provided by the spouses and others is related to the expectant mother's well-being.

In addition, informational support in the form of pre-natal classes related to maternal physical complications is essential to improve physical and mental health after delivery. Mothers who have the support of a companion can benefit from emotional support and practical help in terms of child care and housework. Some respondents mentioned about the prenatal classes to both first time to-be mothers and fathers being offered by some private clinics. Respondent Shariffa, a teacher, noted,

"*Since last month (6 month pregnant), I have been attending free prenatal classes in the private clinic where I go for treatment. This is truly an important aspect that we need to consider especially for first time moms and fathers. Unfortunately, prenatal classes is not given in public hospitals and thus it is not accessible to the mass of the population."*

Support from the child's father was believed to be an important element in the women's sense of control. Participants believe the father should be at loud and listen. Respondent Rachelle, interviewed on the 14th December 2016 noted:

"Support is being there. When I am worried, then he says everything is okay, it will be okay."

The partner's lack of involvement in the disease is interpreted by the respondents as lack of commitment for the child. Respondent Shaina, interviewed on the 15th November 2016, reported:

"Some days, he does not even look at my chart of glucose levels or does not even ask about my health. Then I get super frustrated because it is his child too. If he cares and sees what my glucose values are, then he cares for the child too."

Moreover, due to the risk of low blood glucose levels and insulin, some of the women were totally dependent on support from others. They might even have been obliged to never sleep alone during the night. If in such a situation, the partner chooses his own interests such as work or travelling, a deep sense of disappointment, loneliness and even violation occurred in some of the women. As Nadine, a respondent interviewed on the 17th December 2016 noted:

"It is difficult enough at this age not to being able to stay alone. Being dependent is not an easy thing, you know."

In the absence of conventional conjugal relationships, the respondents who live in single parent households find it difficult to juggle between responsibilities due to the lack of a partner. Kurline, a single parent interviewed on the 15th of November 2016, related the pain she undergoes every day such as financial problems and difficulties. Her partner with whom she was in co-habitation, deserted her when she was four months pregnant. She is still an undergraduate student and does not have any permanent job. She manages with seasonal and part time employment and has just moved to her mother's place who is a divorcee and lives alone. Kurline's main worry is her future child, she stated:

"My child is my priority for the time being. Despite the fact that Amar (her partner) has left, I want to become the mother of his child since I love him a lot. I will do everything to have a healthy baby. I attend my check-ups regularly and my mother helps me financially. Unfortunately, I had to take a break from my studies which I will resume after the birth of my baby."

"Relationships play a vital role in affirming one's sense of meaning and providing social support" (Reiss

et *al*, 2000:487). The respondents agreed that support is important and they always need someone to listen to their problems, feelings and illnesses. One of the respondents Anjalee, a single-parent, during her interview on the 14th December 2016, related her grief,

"*I did not know that I was three months pregnant when we parted ways. Now, I feel very lonely. I have just moved to my mother's place, and things are not the same. I loved my husband very much and I do not understand why he betrayed me. Yes, he had an extra marital affair and now he prefers to live with her. That's why we got separated. I ask God why this has happened and why me?!"*

Thus, the support and concern of a partner during pregnancy can have positive consequences for the mother's desire to carry out their pregnancy. And the lack of support can be destructive for both the expecting mother and future child. To increase their commitment to the pregnancy and childbirth, partners should be more included in the prenatal care process.

VI. Parental Support and Inter-Personal Dynamics

Relationships between adult children and their parents are complex and consist of several independent dimensions, such as love, respect and tradition (Reiss, 1992:254). If these dimensions are well balanced, parents and children would be engaged in more interaction and the relationship would not be based under obligation but rather on mutual respect which is the essence of a long lasting relationship. With regards to the relationships with their parents, almost all the 40 respondents stated that they are in good terms with their parents or parent. 9 out of 40 respondents were in very good terms with their parents and 4 respondents had very good relationships with both their parents and in-laws. Moreover, emotional support which is referred by the researcher here as 'support provided to relieve oneself from any particular anxiety or distress and can range from *mere listening* to *giving advice'*.

The middle-class family usually hold a background which transmits a different 'cultural capital' to their children, teaching them to express their individuality and imagination more freely (Kohn, 1997:45). The respondents reported that they generally had no problems to manage their end of month expenses but sometimes they receive financial help from their parents.

VII. Mother-Daughter Relationships

a) Support from parents: Mother/Father

All interviewees are actually facing some form of emotional distress through a difficult pregnancy and they hold different views about support received from their parents, mostly from their mothers. The respondents showed mote proximity to their mothers as compared to their fathers. They advanced that they feel so close to their mothers and they feel that this maternal bond is eternal. Almost all respondents live far away from their maternal house but they still consider themselves as a member there. They admit that they feel free to go there anytime and are confident about receiving the support they need. As Shaina, a respondent living in a rural area was interviewed on the 14th of November 2016. She denotes,

"*My mother has always considered me as a friend, during my adolescence my best friend was my mother... until now it is the same. I can relate my problems, pregnancy complications, and even my financial problems*".

Drisha, who is 22 years and in her first pregnancy and works as a receptionist, narrated that she usually receive financial support from her mother, aged 59 and who is still working as a teacher,

"My mother still earns a good salary and she voluntarily helps me out whenever I am struggling with financial issues. She also buys me clothes and shoes and I do not have to bother about shopping!"

Moreover, parents are most willing to help in cases of serious or even illnesses. The respondents agree that:

"Sickness brings closeness in the family."

Respondent Tania, a first time to-be mom, aged 21 years was interviewed on the 11th November 2016. She was eight months pregnant and reported that since her first three weeks of her pregnancy, she kept vomiting continuously and could not even stand on her feet. She had to stay at her mother's place for these eight months and was very grateful to her mother who had got out of her way to help her. She said:

"My mother is a real gem. Despite having so many responsibilities at home, she still looked after me so well. She prepared all kinds of food for me every day and I could not even eat one of these meals properly due to continuous vomiting. Both my mother and father would accompany me to the hospital for my check-ups. My father would buy my stuffs and dietetic food regularly."

In addition to the nuclear family units, improved health and life expectancy have added to the complexity of arranging each family vis-a-vis kin and friendship support systems. In addition, the wave of married women with young children returning back to their workplace has challenged the assumption of dependency by wives and has worried those men to continue patriarchal authority. Family support systems, the ways in which family members provide mutually beneficial, reciprocal support were investigated and brought to the attention of academics about three decades ago. Some parents with traditional family members continue with providing support to their grown

children at a critical juncture such as helping them to buy a house or to start a business (Biswas, 2006:92). Respondent Medha, interviewed on the 13th of November 2016 stated,

"My father gave me his lump sum to construct my house after my wedding. He has always helped me in difficult times and today also when I am not well both my mother and father help me a lot in managing my sickness and household."

Respondent Shariffa who works as a clerical officer and was interviewed on the 16th of November 2016 mentioned about receiving a car as a gift from her mother after her wedding. This mode of transport facilitates her greatly and she is still thankful to her mother for that. Another respondent, Neha who was interviewed on the 11th of November 2016 proudly said that as soon as she started having morning sickness and was not feeling well, her mother came to stay with her. The latter helped her fulfilling her domestic responsibilities, accompanying her to the hospital and also provided emotional support to Neha. She stated:

"The presence of my mother itself was a means of encouragement for me. She always uplift my mood, encourages me whenever I am down and helps me in every single way…"

b) Lack of parental support: Mother

Based on the findings in this study, women rely a lot on instrumental support during pregnancy since they are in a difficult situation not being able to stand on their feet and accomplish their daily duties. Most respondents are agreeable to the fact they need someone to help them in daily activities, however they, especially those living in nuclear families, complain that is not always available. As respondent Kaneez, interviewed on the 12th December 2016 conveyed,

"*While I needed someone to stay permanently with me and provide me a helping hand in cooking, washing dishes, laundry and look after my kid, I was very disappointed to notice that not even my mum was ready to help me! Thus my husband appointed a permanent maid who would help me and it really worked. I felt very relieved since my pregnancy was a high risk one and I was to it to carry out my domestic responsibilities.*"

Respondent Rachelle, interviewed in the 14th December 2016 mentioned that she had no one to help her and she has to gather courage to manage with her pregnancy and household duties,

"I am really unwell but I try to cook for my family, drop my daughter to school and attend duty every day. I don't know how long I will be able to do this but am trying my best"

Women reported less positive feelings during their pregnancy as they said that they are doing much more of the housework and childcare than they had expected. Respondent Drisha, interviewed on the 20th November 2016 related,

"I expected to receive help from my mother and husband while pregnant. They know about my health complications but they rarely come to provide support. Especially my mother who keeps herself busy with other priorities!"

An interviewee Jasmine, interviewed on the 19th November 2016 relates that she is not in good terms with her mother who does not understand her. She prefers to seek support from her aunt who is her best friend. The respondents admitted that they always welcome help from their parents and feel discouraged whenever they do not receive support in difficult times. As Shirine, a respondent interviewed on the 21st December 2016 told in her interview,

"*I am very sad and feel so distressed to be in this situation. My mother once told me that I am now married and that her responsibilities towards me is over. She has done enough for me in the past and up to me now to continue my life ahead. This always comes to my mind whenever I am facing any kind of difficulty in my career, raising my child or lately my pregnancy. I hesitate to ask for help and it is my husband who always call her repeatedly to come and help us*." *My mother-in-law works as confidential secretary at the Ministry and she is very formal type, you know, she seldom phones to ask about my health."*

VIII. In-Laws/Daughter-in-Law Relationships

a) Support from in-laws

Respondent Deena who works as a clerical officer and was interviewed on the 16th December 2016, described how her mother in law saw her stressful situation and came to help her voluntarily,

"Despite the fact that we live far from her house, when my mother in law saw my plight she voluntarily came to stay with us. She helps me in everything including household tasks and even wakes up at night to feed my elder son. I am really thankful to her for her determination in helping us. After all she is helping her grandchildren!"

Listening to people's sufferings is also a very important tool in providing support.Housna, a respondent who lives in a rural extended family and was interviewed on the 23rd November 2016 states,

"My mother-in-law is very supportive you know and my father-in-law is even more caring. He is always anxious about my health and keeps asking about my state. He drives me to my appointments and drops my child to school every day."

Another respondent Drisha related how her in-laws would provide support during her pregnancy. She works as a nurse and during her night shifts her father-

in-law would bring her some hot home-made snacks and tea. She related:

"You know, the way my in-laws take care of me, I really don't miss my mother that much. She left this world when I was still a kid and since then, I have been yearning for a mother. Since I have come in this family (in-laws), they look after me as their own daughter and this is very reassuring."

In addition, Mehnaz, a respondent interviewed on the 12th of November 2016 stated:

"When I was around 5 months pregnant, my husband fell ill with strong fits and seizures. He was very stressed due to work overload and many loans that we had lent to build our house. Seeing our plight and especially that of my husband, my mother-in-law who was deputy-head teacher in a primary school, resigned to take care of us. She was very worried about the health of her son and my future child. She gave assistance to our whole family without complaining. For me she is God sent, you know... she is helping us in our difficult times."

b) Lack of support from in-laws

The balance of roles between husband and wife is one of the most important dimensions differentiating the family system of one society from another and from differentiating societies from each other (Barnett, 2004:160). Husbands in joint households and living in patriarchal societies have greater power in terms of rights and freedom than their wives. Power in the Indian family system is primarily derived from one's position in the kinship network rather than from individual characteristics and achievements. This is because of the presumed greater attachment to traditional roles of those joint households where the availability of adult relatives of the husband on whom he can depend for advice and help and as allies in case of conflict with the wife (Baker et al, 2008:881). As respondent Nasreen, who was interviewed on the 14th November 2016 said:

"*Since my husband is two years younger than me, my mother-in-law did not approve this relationship. Till today this is the same. Though I live in the same house, she makes me feel inferior, as if I am an animal! My husband always has the last word and I am like his puppet. I feel very lonely and at times I want to return to my mother's place. I am 7 months pregnant and in a very bad state. I am very worried about my future child due to my pregnancy complications. I pray that he is not diabetic like me..."*

Another respondent Hemlata, who was interviewed on the 18th November 2016 talked about how her mother in law would disregard her pregnancy and her state of health,

"I am in a very bad state and you know I still can't cook for my family. I feel nauseous. My mother in law does not care. She sends food only for my husband and my child. I feel this is very inhumane on her part. And my husband is also very busy, he does not have time to listen to me!"

Respondent Rehana, who is 8 months pregnant and was interviewed on the 16th November 2016, mentioned,

"I live in the house of my father-in-lawwho is a sick person. Since my mother-in-law is no more, I have to cater for all his needs such as food, wash his clothes and so on. These days I am myself not well and I can't really manage on my own. I really need help in my daily activities but my husband does not really believe so. He says he will help me but he does not."

According to the role theory, while the cumulative demands of various roles can result in role strain, available resources may prevent or reduce it (Gatrell, 2007:65). Indeed, it has been recognised that factors such as supportive relationships at home and work have an important bearing on the other extent to which role multiplicity maybe detrimental to an individual's well-being (Dillaway and Paré, 2008:460). Very often when women get back from work in the evening, they has to turn herself into a 'housewife' and get busy in the kitchen or around the house. This becomes even difficult to manage during a high risk pregnancy. Respondent Zabeen, expecting her second child was interviewed on the 19th of November. She said,

"Once I am home, I have to look after the kid and cook food at the same time. Sometimes I feel very tired and want to rest a bit but this is not possible due to all my responsibilities and commitments."

The meaning of parental support varied for the respondents. For some of them, parental support is more of providing guidance, recommending and comprehension rather than material support. Whereas for others (Drisha, Rachelle, Kaneez), parental support is more in the form of material (financial) support. Respondent Mehnaz mentioned that help came to her before she even asked for it. Her mother-in-law is very cooperative and helps her in both household chores and looking after her baby. However, on her side, Deepika revealed that she would never ask for help from her parents since she would not want them to be anxious, although she knew that the latter would provide the essential support to her.

Respondent Saina narrated,

"*We decided to construct our own house before getting married. Once we have moved, I started to feel pressure because we had to manage everything on our own. No one to support us. The tension is more today because I am sick and pregnant, no one to cook my food, look after my kid. It is very tough to handle."*

c) Support from social networks and non-genealogical kin: Friends

Families can provide an opportunity for stability and indirect exchange as normative options (Hansen et

al, 1993: 90). The individually mobile nuclear family may attenuate extended family ties during periods of stress in the movement between social positions. Families today create their own relatives as needed. Friends are called to fill in missing or non-functioning kin. Many respondents reported having friends who really care and mean a lot to them even more than their families. Respondent Priscilla, who was interviewed on the 30th of November 2016 said she prefers to meet friends and rely on them for support since she does not have any in-laws in Mauritius. Her husband is a Chinese native whom she met when she was studying in China. They got married and he came to settle in Mauritius and works as a tourist guide. Consequently, Priscille does not have any in-laws in Mauritius to support and help her whenever when she is in difficulty. She says that only her mother takes care of her and provides support to both of them. She stated:

"These days my mother is not well. She is having some gastric problems. I usually rely on my mother to help me but now she cannot since she is bed ridden. Thus, we rely on my husband's friends and their wives for support and they have now become more than family. My husband's friends are also Chinese who have married Mauritians and settled here. So we have formed a small group of 'good' and reliable friends and help each other as much as possible."

Another respondent Zabeen, was interviewed on the 17th of November 2016 reported,

"I live in the same house of my in-laws but upstairs. They are very nosy and keep a track of everything I do. But they are never ready to help me. They just want to know my whereabouts and gossip around. My mother-in-law always pretends to be very tired and sick whenever she finds that I need help! Thus, I prefer to call my friends especially my best friend who is always ready to help me."

Another respondent, Tania who was rejected by her parents because she married her husband, whom they did not approve the relationship. The couple now live far away from their parents as the husband's family is also not too friendly but more sarcastic and ironical. They prefer to rely on a group of common friends. She was interviewed on the 12th of December 2016 and stated:

"We are like a small family. There is no gossip, jealousy or hatred but only mutual respect, understanding and love. Most of our friends have the same plight as ours that is some of them have either been rejected by their parents or others are not in good terms with their parents/in-laws. We always help each other without hesitation and our unity is our plus factor!"

Moreover, relating to the sensitivity of the issue that is a pregnancy with health complications like diabetes, some respondents mentioned that they feel more comfortable to relate personal issues to a friend rather than to their parent/mother-in-law. Respondent Sarah, interviewed on the 11th December 2016 stated she preferred to discuss about her health issues with her colleague at work who is also her best friend. She stated:

"Poonam, my best friend at work is my confident. It is very easy for me to relate my personal problems as she is very understanding and is a mother of three children."

Another respondent Deepika mentioned:
"Discussing my health issues with my school friend, Anna gives me some relief. We still entertain good friendship since our school days. I think we have an eternal friendship bond. We both understand each other so well. Anna comes to see me almost every day, helps me around the house and sometimes even cooks for me and my husband! No doubt I will also help her in the same way one day if she is experiencing some difficulties in life."

Comparing the findings with research among pregnant mothers without diabetes reveals interesting differences. Living with diabetes is described as a transformational experience. In the present findings, the need to live a normal life, like other pregnant women was obvious. Women with Type II gestational diabetes (GDM) had difficulty in daring to hope. Thoughts and plans for the future and the child's arrival were rare and absent. This behaviour seemed to be a kind of defence against the threat of sorrow and uncertainty about an unhealthy child. This study's findings make it clear that life for pregnant women with GDM, as for all humans is based on relationships (0). Life is intersubjective ( ) and thus social support is of great importance. Shared control includes a woman's need and desire to take responsibility and to be coached or supported by health professionals, relatives and employers. Women are involuntarily controlled when health professionals act as a controlling factor, relatives deny support or increase worry.

Pregnant women with GDM is found through this study as extremely vulnerable. Behaviours of health professionals, such as nurses, midwives and physicians and of relatives, friends and employers influenced the women. The latter should encourage her to master the disease and the overall goal should be to support the pregnant women to live a life that is best suited for both the child's health and her own well-being. This includes an open caring relationship where the individual women is understood and supported, empowered to strive for normal glycaemia, and encouraged to be reconciled with her disease. It also includes informing her partner and other significant persons about her need for support.

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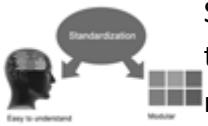

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Note :

"

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- In case, the chairperson needs to be replaced then consent of 2/3rd board members are required and they are also required to jointly pass the resolution copy of which should be sent to us. In such case, it will be compulsory to obtain our approval before replacement.
- In case of "Difference of Opinion [if any]" among the Board members, our decision will be final and binding to everyone.

"

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1. General,

2. Ethical Guidelines,

3. Submission of Manuscripts,

4. Manuscript's Category,

5. Structure and Format of Manuscript,

6. After Acceptance.

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The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled 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 with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose 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 sound written Procedures segment allows a capable scientist to replacement 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 for the least amount of information that would permit another capable scientist to spare 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 object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text 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:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not 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 - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in 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 a 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. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise 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 in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to 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 part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

Discussion:

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a 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 implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly 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 with prospect, and let it drop at that.

- Make a decision if each premise is supported, 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 the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One 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 available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to generally acknowledged facts and main beliefs in present tense.

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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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