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Correlation of Type-2 Diabetes Mellitus with oxidative damage and Cancer

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SUMMARY
The prevalence of diabetes mellitus (DM) is growing exponentially worldwide at an epidemic proportion . This chronic disorder has a negative effect on most metabolic pathways and contributes to diabetes complications . Persistent hyperglycemia induces oxidative stress and is suggested to play a prominent role in T2DM.

Background
The objective of this review is to summarize the findings of previous published research that investigated the relationship between diabetes mellitus and cancer.Current study aimed to correlate the status of biochemical indices in reference to increased glycosylated hemoglobin in T2DM subjects.

Methods
i. Enzymatic HbA1c assay method
ii. Hexokinase method
iii.Enzymatic method of triglycerides and high density lipoprotein-c
iv.Thiobarbituric acid method
v.Chemiluminescence method

Results
The present study specified correlation in glycosylated hemoglobin,glucose,triglycerides,high density lipoprotein-C,malondialdehyde and CA 19-9 as compared to control group and T2 DM group based on statistical analysis.In the present study,control group and study group values of biochemical parameters significantly increases glycosylated hemoglobin (%) as mean >>5.39(0.38)<< in control group and >>7.62(1.68)<< in T2DM group($p<0.001$) glucose (mg/dL) increases as mean >>95.56(21.23)<< in control group as compared to >>160.39(97.89)<< ($p<0.001$) inT2DM group.Both groups include total number of 117 patients. Mean values of triglycerides (mg/dL) were significantly increased >>1.81(1.12)<< as compared to control group >>1.39(0.85)<<($p<0.05$).The level of high density lipoprotein-(mg/dL) increases significantly with mean value of >>1.59(0.62)<< in control group as compared >>1.37(0.35)<< to T2DM group($p<0.05$),malondialdehyde (nmol/µL) level increases <<0.31(0.09)>> as compared to T2DM group>>0.72(0.48)<< ($p<0.001$) and CA19-9 (U/mL) level increases >>12.54(9.43)<< as compared to T2DM group >>19.87(17.12)<< ($p<0.005$).

Conclusion
It has to be a correlation in this study with the reference of biochemical parameters which linked oxidative damage and cancer in type-2 diabetes mellitus patients with the increased levels of malondialdehyde and CA19-9 estimated in the patients.

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Abstract:-The prevalence of diabetes mellitus (DM) is growing exponentially worldwide at an epidemic proportion . This chronic disorder has a negative effect on most metabolic pathways and contributes to the pathophysiology of diabetes complications . Persistent hyperglycemia induces oxidative stress and is suggested to play a prominent role in T2DM. The objective of this review is to summarize the findings of published research that investigated the relationship between diabetes mellitus and cancer.Current study aimed to correlate the status of biochemical indices in reference to increased glucose in T2DM subjects . A total of 66 subjects consisting of control (33) and T2DM patients (33) were included.117 subjects have studied in previous published research on "Linking of Type-2 Diabetes Mellitus with Oxidative damage and Cancer".Two groups were created based on levels of HbA1c(I-5.39±0.38,II-7.62±1.68).FBG(p value<0.001),TG(p value<0.05),HDL-C(<0.05),MDA (p value<0.001) and CA19-9(p value 0.005) were measured. Level of significance predicts hyperglycemic status influenced oxidative damage and pancreatic

cancer.This study is conducted in Meerut in the year 2021.

Abbreviations

DM-Diabetes Mellitus, SOD-superoxide dismutase ,CAT-catalase , GLT-glutathione,RNS- reactive nitrogen species, Nf-κb- nuclear factor kappa b, p38 MAPK-p38 mitogenactivated protein kinases, JNK/SAPK-stress-activated protein kinase/c-Jun NH(2)-terminal kinase,PKC- Protein Kinase C, AGE/RAGE-advanced glycation end product/receptor for AGE,ROOH-Reactive Hydroperoxides, GLUT-4-Glucose Transporter, PPAR-γ-peroxisome proliferator-activated receptor gamma), CEB/Ps-CCAAT enhancer-binding proteins,nuclear factor-1, p85, HIF-1α-hypoxia-inducible factors alpha, MEF2-myocyte enhancer factor 2, 8-OHdG- Hydroxydeoxyguanosine ,T2DM-Type-2 Diabetes Mellitus,PKC-Protein Kinase C,HbA1c-Glycosylated Hemoglobin, FBG-Fasting Blood Glucose,TG-Triglycerides,HDL-C-High Density Lipoprotein,MDA-Malondialdehyde,CA19-9-Cancer Antigen.

Purpose

The purpose of present study is to determine the correlation of hyperglycemic subjects with oxidative damage and risk of cancer.

I. INTRODUCTION

Diabetes mellitus (DM) is characterized by disruption in glucose homeostasis and defects in insulin action on many target tissues including liver, muscle, pancreas and adipose.Diabetes is a common metabolic abnormality and is classified as two types: type I is pathologically based on the deficiency in insulin secretion by pancreatic islet cells and type II is characterized by insulin-resistance which renders target cells unable to adequately respond to insulin and thus unable to use blood glucose for energy [1–3]. To compensate, the pancreas makes increasingly more insulin, resulting in insulin resistance syndrome which includes obesity, high blood pressure, high cholesterol and eventually type 2 diabetes [2,3]. From a survey of the International Diabetes Federation, there were 366 million people with diabetes in 2011 and the total number is expected to rise to 552 million by 2030. Type 1 diabetes accounts for 5%–10% of the total cases of diabetes and type II diabetes accounts for 90%–95% [4].Diabetic complications result in considerable morbidity and mortality leading to major healthcare delivery costs [5]. Although there are several studies to elucidate the molecular mechanisms underlying the development of diabetes complications [6-9], their precise pathophysiology is not completely understood . One of the major mechanisms for the development of diabetes complications is through oxidative stress [9]. Oxidative stress develops when the rate of free radical generation exceeds the antioxidant defense systems resulting in the toxic effects of free radicals [10, 11]. Free radical species are important physiological components in biological homeostasis [12, 13], but 95% of patients with diabetes and is mainly linked to inadequate response to insulin (reduced insulin sensitivity) and insulin resistance in peripheral tissues [17].

Free radicals are active biomolecules which are physiologically generated during metabolic pathways and/or by immune cells [21]. Free radicals have physiological roles in many molecular pathways including those of cellular signaling,synaptic plasticity, memory formation, defense against invader pathogens, cell-cell interactions, cell growth, autophagy,apoptotic processes and aging [21–24]. When free radical generation increases above the physiological range, it overcomes the antioxidant mechanisms of cells and results in oxidative stress [23, 24]. Most biologic cells have an intrinsic defense mechanism involving various enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione(GLT), which protect cells against free radical attack [25].Free radicals are active derivatives of either the oxygen molecule such as reactive oxygen species (ROS: hydroperoxyl,superoxide, hydrogen peroxide, and hydroxyl radicals) and nitrogen molecules such as the reactive nitrogen species (RNS) peroxynitrite [26]. Some heavy metal derivatives such as iron (ferric) and copper have free radical properties [27].

These hyperactive elements have unpaired electrons in their router layer of molecules and thereby can bind with other biomolecules and modify them [21, 28]. They can oxidize proteins, lipids and nucleic acids and produce toxic byproducts leading to tissue dysfunction [29, 30]. Also, they alter the structures of biologic molecules and even break them[31]. DNA breakage is a known effect of oxidative stress ,which affects the expression of most genes and cell survival[28]. Free radicals not only have direct deleterious effects, but also can indirectly damage cells by activating a variety of stress-sensitive intracellular signaling pathways such as Nf-κb (nuclear factor kappa b), p38 MAPK (p38 mitogenactivated protein kinases), JNK/SAPK (stress-activated protein kinase/c-Jun NH(2)-terminal kinase), hexosamine pathways, PKC (protein kinase C), AGE/RAGE (advanced glycation end product/receptor for AGE) interactions and sorbitol synthesis [32]. The various biomarkers for oxidative stress in patients with

diabetes include malondialdehyde (MDA), total cholesterol, and reactive hydroperoxides(ROOH) [28]. Oxidative stress has pivotal roles in the pathophysiology of various complications of diabetes through lipid peroxidation, DNA damage and mitochondrial dysfunction [26, 36, 44, 45]. It is also closely involved in many other pathological conditions as well as age-related disorders such as cardiovascular diseases, chronic obstructive pulmonary disease, chronic kidney disease, neurodegenerative diseases and cancer. Aging and its related disorders are identified as the progressive loss of tissue function through differing mechanisms including elevated free radical species. Many scientists believe that the oxidative stress theory is the major cause of aging and age-related complications [36]. Hence, maintaining the normal state of redox biology is of importance to prevent oxidative stress-induced complications as well as insulin resistance [37]. Oxidative stress impairs beta-cell function via several molecular mechanisms [57, 64, 65] [56–62]. It markedly reduces insulin production, impairs inclusion of proinsulin vesicles into the plasma membrane, and reduces their exocytosis in response to glucose into the circulation [58, 59, 60]. Itcan also induce apoptotic processes in the pancreatic cells leading to death and loss of beta cells [60, 67, 68]. A series of proapoptotic agents are highly sensitive to oxidative stress and can activate the apoptotic process in the pancreatic cells [62–64]. Moreover, an overload of free radical species has a negative effect on metabolic pathways in the beta cells and impairs KATP channels leading to lower insulin secretion [47, 60]. The free radicals impair KATP channels by binding to their SH residues [57–59], confirmed by studies demonstrating that genetic knockout models of KATP channels in beta cells resulted in their protection against oxidative stress [61].Higher concentrations of free radicals inhibit the nuclear transcription factors involved in insulin gene expression as Pdx-1 (insulin promoter factor 1) and MafA (a transcription factor) thereby reducing insulin production at the DNA level [62]. Wang and Wang in 2017 reported that oxidative stress induced molecular pathways such as Nf-κb, JNK/SAPK, p38 MAPK, and hexosamine pathways.These stress-activated signaling pathways have a pivotal role in beta-cell dysfunction [63]. Free radicals can also activate TLRs (toll-like receptors) that in turn impair beta-cell function [66, 67]. Oxidative stress induced mitochondrial dysfunction in the beta cell is another possible molecular mechanism between oxidative damage and beta-cell dysfunction [48].Although free radicals have a physiological role in beta cell proliferation, excess of free radicals will disturb the beta-cell neogenesis [62, 68, 69]. Miceli and coworkers in 2018 found that oxidative stress markedly disturbed beta cell function in an in vitro experiment [68]. They imposed oxidative stress on rat INS-1E and mouse MIN6 beta-cell lines by exposure to 200 μM hydrogen peroxide (H2O2) and found that glucose-stimulated insulin secretion was significantly reduced in these cells [70]. Moreover, this event was completely reversed by using carnosine as an antioxidant [69]. Oxidative stress decreases the proliferation and differentiation of beta cells by complex interactions with different factors such as Pdx-1, Nkx6.1, Ngn.3, FOXO, and MafA[59,70, 71]. These transcriptional mediators are highly sensitive to the redox imbalance and exposure to higher levels of free radicals negatively modulates the proliferation of the beta cell [70,72].Oxidative stress can reduce GLUT-4 content by negatively effecting its gene expression by impairing the binding of nuclear factor to the insulin responsive element of the GLUT-4 promoter in 3T3-L1 adipocytes. Pessler et al. in 2001 exposed 3T3-L1 adipocytes to micro molar H2O2 concentrations and developed oxidative stress in these cellsand then were detected the GLUT-4 expression in these tissues[82]. They found that peroxide hydrogen-induced oxidativestress markedly downregulated GLUT-4 in 3T3-L1 adipocytesand thereby, reduced glucose entering into the cells[78]. Also, Fazakerley et al. in 2018 conducted a study confirmingoxidative stress decreased the GLUT-4 translocationtoward the cell membrane [81]. They induced mitochondrialoxidative stress using a mitochondria-targeted paraquat(a selective peroxide generation inducer for mitochondria),in adipocytes and myotubes of mice and observed that oxidativestress markedly suppressed GLUT-4 trafficking andthereby induced insulin resistance in these tissues [87].Prolonged oxidative stress can suppress the transcriptional factors involved in the GLUT-4 expression such as PPAR-γ (peroxisome proliferator-activated receptorgamma), CEB/Ps (CCAAT enhancer-binding proteins),nuclear factor-1, p85, HIF-1α (hypoxia-inducible factors alpha), MEF2 (myocyte enhancer factor 2), and Nf-κb [80, 82–84]. It could also suppress micro RNAs involved in the GLUT-4 expression such as miR-21a-5p, miR-222-3p, miR-133b-3p, miR-10b, miR-106b-5p, miR-29c-3p, and miR-133a-3p, although further research is needed to clarify this mechanism[83–86]. Moreover, a wide range of oxidativestress-induced factors and byproducts such as p38 MAPK, JNK/SAPK, PKC (protein kinase C), sorbitol and hexosamine are all activated by oxidative damage and can suppress

GLUT-4 expression [27]. Hence, reduction of GLUT-4 expression/localization is one of the main molecular mechanisms by which oxidative stress induces insulin resistance and contributes to the development of DM [13].Diabetes mellitus type 2 (T2DM) designated by multiple etiologies is portrayed by chronic hyperglycaemia resulting due to impairement in metabolism of major biomolecules oftenly due to ROS (reactive oxygen species). ROS are maintained within limits under normal physiological conditions by scavenging systems of antioxidants and antioxidant enzymes. The imbalanced redox status arose due to hyperglycemic state leads to damage to biomolecules like lipid, peptides including DNA. Damage to DNA is known to be associated as a cause in varied diseases including cancer (Halliwell, 1994). ROS, the molecular oxidants are known to trigger the development of cancer as DNA is the probable target of the oxidative attack. Apurinic DNA, oxidized nitrogenous bases, excision of ss or ds DNA are few of the examples of oxidatively induced DNA damages. Free radical can act on the nitrogenous bases and chromatin leading toaltered gene expression. Similar array of events could occur in tumour suppressor genes and trigger cancer (Sova et al., 2010; Lee and Chan, 2015). Therefore it is proposed that diabetes subjects are at risk of different types of cancer effecting the major organs likestomach, liver, lung, pancreas, colorectum, breast and other sex organs (De Beer and Liebenbergm, 2014). Among different types of oxidative damage to DNA, 8 Hydroxydeoxyguanosine (8-OHdG) is a universal marker measurable by ELISA technique.

Association of diabetes with cancer and the alarming number of diabetes among adult population is an eye openor to all diabetologist's to explore and find new preventive measures that couldreduce the morbidity/mortality risk in these patients.The interrelation between pancreatoma and diabetes is intricate due to existence of two forms of diabetes with different pathophysiologies. Type 1 DM association with pancreatic cancer is notified as unrelated etiologies by many researchers. While some study have reported absence of correlation between diabetes and pancreatomas (Hjalgrim et al, 1997;Frye et al., 2000), numerous other researchers suggested higher risk of pancreatic cancer due to insulin resistance in diabetes subjects (Wang et al., 2003). However, the link between T2DM and cancer is still debatable. Recently,a meta-analytic study reported 1.2 fold increase risk of breast cancer among T2DM (Vigneri et al., 2009). Hence there is need for an hour to assess the levels of few prominent cancer biomarkers as prognostic tools in diagnosis of different types of cancer in T2DM patients. Currently number of cancer biomarkers (CBs) are available to be used in detection or diagnosis of possible cancer risks.Few of the circulating CBs like Carcinoembryonic antigen (CEA), alpha-feto protein (AFP), CA125 are of prime significance in cancer research. CEA is one of the most commonly used cancer marker (Park et al., 2011). It is expressed at multiple sites including the pancreas, lung, prostate, ovary, breast and colon (Malati, 2007).Tumor biomarker CA 19-9 overexpression has been documented in patients with pancreatoma and cancer of biliary tract in previous reports. CA 19-9 also is raised in other types of cancers like gastric, oesophageal, colorectal, hepatocellular and ovarian cancers (Locker et al., 2006;Perkins et al., 2003). Another significant cancer markerwhich is used in diagnosis of cancer of liver, testicles and ovary is alpha-feto protein (AFP) (Li et al., 2017). Recently, a tumor marker plasma cancer antigen (CA)-125 related to heart failure following myocardial infarction is identified (Sekiguchi et al., 2017). There also exists a strong link between glucose levels and increased risk for breast carcinogenesis (Dong and Qin, 2011).

T2DM is a diversified disease with varying levels of increased glucose. Our goal in this case controlled study was not just to compare between normal and diabetes subjects but instead diabetic individuals with HbA1c above cut off of 6.5% were compared to normal non diabetic patients with glycated Hb < 5.7%[88].

II. MATERIALS AND METHODS

Two hundred and fifty volunteers participated in the study.Out of 150 patients 117 were studied in my previous research.Depending upon the baseline parameters and physician diagnosis33 subjects were selected by stratified sampling method and grouped into two groups using cut off value of HbA1c 6.5% as per American Diabetic Association (2014).The present study for research has to be conducted in CSSH,SMC,SVSU,Meerut for 33 individuals of healthy control group and 33 patients of Type-2 Diabetes Mellitus.117 patients in previous study and 33 patients in present study.They have age group of 42-68 years.

Quantitative analysis of glycosylated hemoglobin (HbA1C)-Enzymatic HbA1c assay method

Principle

Oxidizing agents in the lysis buffer react with the blood sample to discard low molecular

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weight and high molecular weight signal interfering substances. After lysis, the whole blood samples are subjected to proteolytic digestion. This process releases amino acids, including glycated valines, from the hemoglobin beta chains. The Direct Enzymatic HbA1c Assay glycated valines serves as substrates for a specific recombinant fructosyl valine oxidase (FVO) enzyme. The recombinant FVO specifically cleaves N-terminal valines and then produces hydrogen peroxide in the presence of selective agents. This is measured using a horseradish peroxidase (POD) catalyzed reaction and a suitable chromagen. The signal produced in the reaction is used to directly report the percentage HbA1c of the sample using a suitable linear calibration curve expressed in %HbA1c.

Quantitative analysis of blood glucose-Hexokinase method

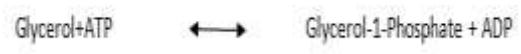
Principle

The enzyme hexokinase (HK) catalyzes the reaction between glucose and adenosinetriphosphate (ATP) to form glucose-6-phosphate (G-6-P) and adenosine diphosphate (ADP). In the presence of nicotinamide adenine dinucleotide (NAD), G-6-P is oxidized by the enzyme glucose-6-phosphate dehydrogenase (G-6-PD) to 6-phosphogluconate and reduced nicotinamide adenine dinucleotide (NADH). The increase in NADH concentration is directly proportional to the glucose concentration and can be measured spectrophotometrically at 340 nm.

Quantitative analysis of triglycerides & high density lipoprotein-CEnzymatic method

All samples will assayed and lyophilized until needed. Triglycerides were assayed with fully automatic analyzer enzymatically.

Principle-Triglycerides are estimated in the presence of glycerol kinase and pyruvate kinase followed by a series of reactions-glycerol kinase pyruvate kinase pyruvatees of 3 ml of triglycerides reagent in a cuvette with a 10 mm light path, add 50 micro litres of serum, mix and incubate at 30° C for 10 min. Read the absorbance of sample at 340 nm with distilled water as a blank.



Quantitative analysis of malondialdehyde

Principle

MDA in the catabolite of lipid peroxide can react with thiobarbituric acid and produce red compound,which has a maximum peak at 532 nm.

Chemicals and Reagent-Thiobarbituric acid (TBA) 99%,malondialdehyde tetrabutylammoniumsalt (MDAsalt) 96% pure and methanol 99.8%, Glacial acetic acid (99–101% pure). Ultrapure deionized double distilled water with less than 5mΩ was used. All other chemicals and reagents were of an analytical standard with high purity.

Preparation of TBA Reagent- The standard solution of 4.0mM of TBA was prepared in glacial acetic acid. For this purpose, 57.66mg of TBA was dissolved in 100mL of glacial acetic acid. Fresh solution of TBA was prepared every day.

Preparation of MDA and Calibration Standards-Standard stock solution of MDA (1mM) was prepared in glacial acetic acid. MDA (31.35mg) was accurately weighed and dissolved in 100mLsolvent. From the stock solution, different concentrations of 0.1, 0.2, 0.4, 0.6, and 0.8mM were prepared.

Analytical Procedure- The standard MDA solution (1 ml) was taken in a 10mL test tube and mixed with TBA (1 ml).The mixture was heated in a boiling water bath at 95∘C for 60 minutes. The test tubes were cooled at room temperature and absorbance was measured at 532 nm using UV-visible spectrophotometer.

Quantitative analysis of CA19-9 - Chemiluminescence method

Principle

The TM-CA19-9 ELISA kit is a solid phase enzyme linked immunosorbent assay based on the sandwich principle. The microtiter wells are coated with a monoclonal antibody directed towards a unique antigenic site of the CA19-9 molecule.

An aliquot of patient sample containing endogenous CA 19-9 is incubated in the coated well with assay buffer.After a washing step a second incubation follows with enzyme conjugate, which is an anti-CA 19-9 antibody conjugated with horseradish peroxidase. After incubation the unbound conjugate is washed off.The amount of bound peroxidase is proportional to the concentration of CA 19-9 in the sample. Having added the substrate solution, the intensity of colour developed is proportional to the concentration of CA 19-9 in the patient sample.

Reagents

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12x8 (TM E-4531 Microtiterwellsbreak apart) strips, 96 wells; Wells coated with anti-CA 19-9 antibody (monoclonal).

Standard

Cat.no.	Standard	Concentration	Volume/Vial
TM E-4501	Zero Standard	0 U/mL	3 ml
TM E-4501	Standard 1	15 U/mL	0,5 ml
TM E-4501	Standard 2	30 U/mL	0,5 ml
TM E-4501	Standard 3	60 U/mL	0,5 ml
TM E-4501	Standard 4	120 U/mL	0,5 ml
TM E-4501	Standard 5	240 U/mL	0,5 ml

III. RESULT

The baseline characteristics of the studied groups are depicted in Table II. The mean values sharing the same superscripts differ significantly at 0.001 level. Both groups include total number of 61 males and 56 females. Mean values of FBG, HbA1c, TG, HDL-C were significantly increased in T2DM group compared to control.Tableshows the mean values of oxidative stress and cancer biomarkers in the aforementioned groups, mean values with different superscripts alter at 0.01 level of significance. Enhanced levels of MDA was observed in T2DM group compared to control at P < 0.001. Serum levels of CA 19-9 in T2DM compared to control.

Furthermore, to study the correlation between levels of HbA1c,markers of oxidative stress and cancer, the groups were divided based on levels of HbA1c.

Table I

Demographic data

Mean age		Cases	Control
59 ± 13.34	Males	17	15
54 ± 12.78	Females	16	18
Hypertensive	Yes	70 %	30 %
	No	30 %	70%
Smokers	Yes	70 %	30 %
	No	30 %	70 %
Alcoholics	Yes	70 %	30 %
	No	30 %	70 %

Table II

Subject	No.of patients	HbA1C (%)	Glucose (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	MDA (nmol/µL)	CA 19-9 (U/mL)
Control	33	5.39±0.38	95.56±21.23	1.39±0.85	1.59±0.62	0.31±0.09	12.54±9.43
T2DM	33	7.62±1.68	160.39±97.89	1.81±1.12	1.37±0.35	0.72±0.48	19.87±17.12
P value	p<0.001	p<0.001	p<0.001	p<0.05	p<0.05	p<0.001	p<0.005

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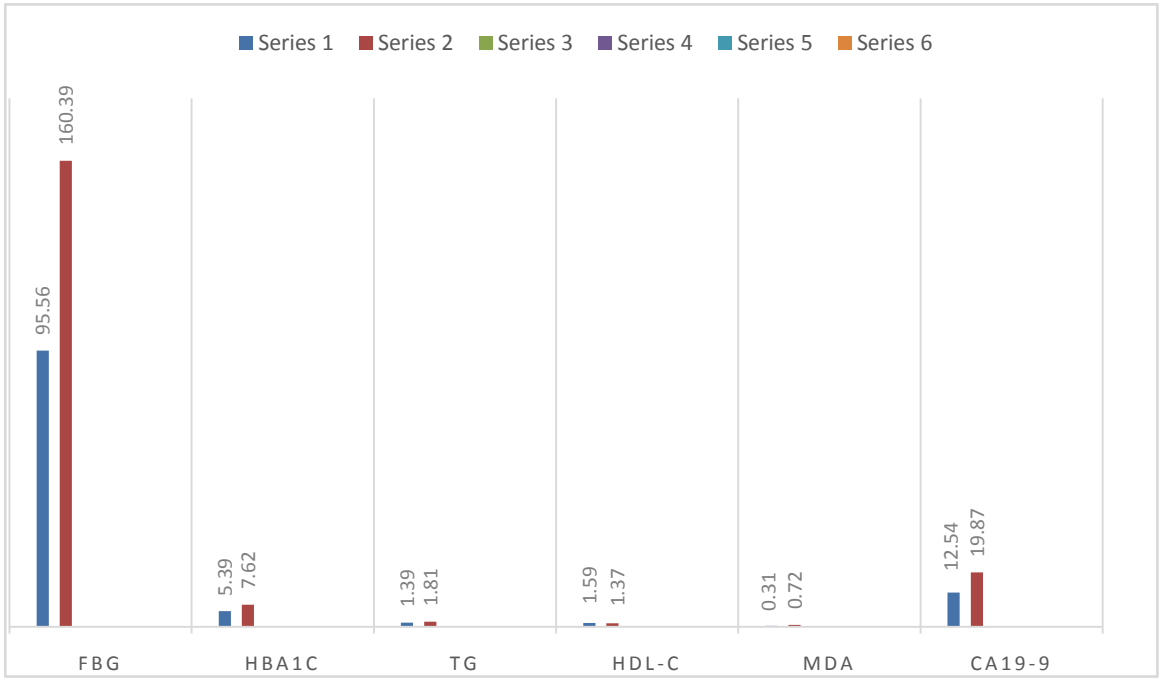

Graph-Comparision of biochemical parameters in control group Vs T2DM group

IV. DISCUSSION

There are several studies to elucidate the molecular mechanisms underlying the development of diabetes complications [8-10].One of the major mechanisms for the development of diabetes complications is through oxidative stress [11]. DNA breakage is a known effect of oxidative stress,which affects the expression of most genes and cell survival[26]. Oxidative stress has pivotal roles in the pathophysiology of various complications of diabetes through lipid peroxidation, DNA damage, and mitochondrial dysfunction [6, 26, 34, 35]. The imbalanced redox status arose due to hyperglycemic state leads to damage to biomolecules like lipid, peptides including DNA. Damage to DNA is known to be associated as a cause in varied diseases including cancer (Halliwell, 1994).Various epidemiological and clinical studies portrayed DNA damage associated with poor glycemic control and its complications, however none had analyze oxidative stress parameters in connection with detected DNA damage in diabetes subjects. With regard to HbA1c levels in three tertiles (range<6.5% to >7.5%) confounding results were obtained in our study.HbA1c did not reveal any significant correlation with oxidative stress parameter, antioxidant enzyme activities and DNA damage. Association between diabetes and various types of cancer most notably the pancreatic cancer has been perceived. Unraveling the link between HbA1c, oxidative stress and cancer in diabetic subjects ,analysis of some cancer biomarkers was performed to elucidate any possible correlation that exists between these markers.Potential cancer markers like CA125, CEA, AFP CA15-3, CA19-9and prolactin were analyzed in serum of studied population. Serum Numerous other researches suggested higher risk of pancreatic cancer due to insulin resistance in diabetes subjects (Wang et al., 2003). Tumor biomarker CA 19-9 overexpression has been documented in patients with pancreatoma and cancer of biliary tract in previous reports.

Serum values for CA 19-9, CEA increased whereas levels of AFP and prolactin decreased in T2DM compared to control. CA 19-9, CEA was found to increase significantly ($p < 0.05$) whereas PRL decreased significantly at $p < 0.001$ in T2DM patients. Altered levels of CA15-3 and AFP were non-significant. The levels of CA125 were weakly significant among the groups. In contrast to our finding, increased values of CA125, CA15-3 and decreased CEA in T2DM patients was reported by Turgutalp et al. (2013). Homology to the finding of Turgutalp et al. (2013) we observed increased values of CA 19-9 and decreased AFP in T2DM subjects. Verily, elevated values of CA 19-9 obtained in current study are in agreement with earlier studies but conflicting results was observed in HbA1c association with CA19-9 in T2DM subjects (Gul et al., 2011). CA19-9 levels although found to increase in T2DM in our study yet the correlation with HbA1c was not conspicuous. The paramount in the present study was none of the

cancer biomarkers exhibited significant association with HbA1c except for PRL.A study by Uygur-Bayramicli et al. (2007) observed increased values of CA 19-9 levels in T2DM patients than controls but analysis of correlation between CA19-9 with glycemic control was not investigated. Also, contradictory evidences on the role of cancer markers in T2DM were reported. Few studies exhibited significant correlation of HbA1c with FBG and CA 19-9 whereas some did not (Benhamou et al., 1991;Banfi et al., 1996). Higher levels of CEA observed in the present work are contradictory to that reported in previous study (Turgutalp et al., 2013).A previous study in Qassim, KSA involving T2DM females have CA19-9 is identified as a vital diagnostic marker/indicator in different types of malignancies including gastrointestinal, hepatobilliary and urothelial cancer, most notably pancreatoma (Locker et al., 2006; Kim et al., 2009). Similar to our findings, previous report have suggested higher CA19-9 levels in T2DM. Increased CA19-9 could be a sequel of deprived metabolic compensation and poor glycemic control (Shimojo et al., 1990)[88].Previous studies have provided substantial evidence of associations between T2DM and risks of cancer in hepatocellular, biliary tract, gallbladder, pancreas, gastrointestinal, kidney, bladder, lung, thyroid, breast, ovarian, endometrial, oral, leukemia, glioma, and melanoma [89, 90–95]. Among them, the highest risks has been demonstrated for colorectal cancer [96], hepatocellular cancer [97], or pancreatic cancer[98-99].In the review of present study biochemical parameters in T2DM group such as glycosylated hemoglobin increased,triglycerides increased,high density lipoprotein decreased,malondialdehyde increased and tumour marker CA 19-9 increased significantly as compared to control group.

V. CONCLUSION

In conclusion, data obtained in thisresearch suggested that oxidative stress and cancer biomarker are increased in diabetes. There is a imbalance between the markers of oxidative damage and cancer in the present study.It imparts a vital role in linking of Type-2 Diabetes Mellitus with oxidative damage and cancer.

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