Research Article

# Molecular Association of Diabetes Mellitus with Different types of Cancer from Population of Lahore

**Snobia Munir*** **and Samreen Riaz**

Department of Microbiology and Molecular Genetics, University of the Punjab, Pakistan

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**Corresponding author:**
Snobia Munir,
Department of Microbiology and Molecular Genetics, University of the Punjab, Pakistan, Tel: 92-3158269694;
Email: snobiamunir@yahoo.com

## ABSTRACT

Million people die of diabetes and different types of cancer every year. Current study include effects of major risk factors, as hyperglycemia and obesity are novel risk factors contributing both cancer and diabetes and biochemical pathways in association with these two diseases. Diabetes mellitus can enhance risk of a varied range of tumors, for instance pancreas, liver, early gastric, lung, prostate, breast, acute myeloid leukemia and colorectal cancer. Scientists have substantiated the link of diabetes with increased prevalence, augmented progression & improved cancer aggression. 200 samples of Diabetic and 200 Cancer patients were collected from the Endocrinology & Oncology department and wards of Jinnah Hospital Lahore and 100 normal healthy control subjects were selected. In order to evaluate the level of proteins, the serum level of samples is initially estimated and tested by different standard procedures including HPLC assay of each sample. Results from all assays demonstrated the increased level of proteins in the diabetic & cancer group compared to the normal population. The findings may recommend sodium dodecyl sulfate poly acrylamide gel electrophoresis as an effective method of early detection for disease. The physical and biochemical parameters of all the 500 individuals were noted. The biochemical parameters like blood fasting sugar, Body Mass Index (BMI), HbA1c, liver tests were highly raised and statistically significant high level of proteins were observed in patients suffering from diabetes & cancer.

## INTRODUCTION

Two complicated, varied, chronic and possibly deadly illnesses are diabetes and cancer. Cancer is the 2nd main cause of death, while the 7th major cause of demise is diabetes [1,2]. Type 2 Diabetes Mellitus (T2DM) is the common lifelong metabolic disease with severe acute and chronic complications leads to substantial deaths globally [3,4].Cancer is the major cause of mortality around the globe that accounts 9.6 million deaths. International agency for research on cancer evaluated 1:5 males and 1:6 females worldwide that acquire cancer throughout their lives [5].Pakistan is in seventh place for Diabetes Mellitus and 11.77% population suffers from Diabetes Mellitus [2].

According to report of International Diabetic Federation (IDF) published in 2015, 415 million people are suffering from diabetes mellitus and will rise to 642 million by 2040. Type II Diabetes can boost the possibility of different cancer types, like pancreas, liver, ovarian, prostate, lung, breast, acute myeloid leukemia and colorectal cancer. People with diabetes have about 30% higher relative menace of cancer than

non-diabetic people. Persistent hyperglycemia could cause permanent damage, dysfunction, and failure of several parts of the human body, such as eyes, heart, nerves, kidneys and blood vessels [6].18% people with cancer have pre-existing diabetes. Cancer and diabetes patients have high death and complication rates and are more likely to be hospitalized than cancer patients without diabetes [7,8].

Hyperinsulinemia was suggested as fundamental connection between diabetes and cancer. Insulin enhances cell proliferation via a small path comprising of insulin receptor or insulin-Like Growth Factor (IGF)-I receptor's direct activation and main pathway inhibits Insulin Growth Factor binding proteins (especially IGFBP-1 and IGFBP-2), that leads to augmented insulin growth factor-I [9,10]. Overweight individuals have a greater risk of multiple cancers compared to individuals whose BMI is within standard limit [11]. Roughly 41 million kids (under 5 years) were discovered to be obese in 2016; and around 1.9 billion adults (18 years and older) were investigated to be overweight globally, 650 million of whom were obese [12]. Expression of Fat Mass and Obesity-associated protein (FTO) helps in diagnosis and treatment of diabetes and strongly identifies a common genetic variation with the Body Mass Index (BMI). Over-expression of the FTO raises food intake, contributing to obesity, which is one of the main cancer incidences threats. Adipose cells causes insulin resistance and growth factors (leptin, TNF, andIL-6), intensify insulin in diabetics that leads to complications including cancer [13]. Tumor protein D52 belongs to the TPD52-like family of proteins and plays various roles in different types of malignancies [14]. TPD52 (CRHSP-28) is a charged, acidic, cytosol and membrane protein present at periphery and its over expression was reported in several cancers like breast, lung, pancreatic, prostate, colon, ovarian, B cell and cancer cell lines [15,16].

Drugs that lower insulin, like met form in, may be helpful in reducing insulin resistance concentrations, body weight, and improves cancer results in patients with obesity and type II diabetes. Several studies identify the relation between metabolic and anti-inflammatory effect of met form in on cancer-free survival. Drugs to treat diabetes can also be used in cancer therapeutics along with certain phytochemicals as they are beneficial in preventing cancer by suppressing the signaling pathways. Recent advancement has shown that met form in may be involved in suppression of cancer through the indirect instigation of Adenosine mono phosphate-activated protein kinase, an important element for adenosine tri phosphate and adenosine mono phosphate balance of cell and helps in activation of cancer suppressor genes like LKB1. Experiments demonstrate that met form in prevents tumor and minimize risk of cancer. Met form in therapy in diabetic patients is related with relatively less chance of cancer and prevents deaths due to cancer [17]. Diabetes Mellitus and obesity has a strong link with cancer. The main objective of study is to develop awareness among individuals having diabetes and various types of cancer from the risk factors contributing it.

## METHODS

### Study Area

We carried our research from March, 2019 to December, 2019 at the Department of Microbiology and Molecular Genetics, University of the Punjab and Jinnah Hospital Lahore, Pakistan.

### Approval from Ethical committee

The committee of ethics of Jinnah Hospital Lahore has endorsed the reliability of this research work having a reference no. 22919/JH and the Departmental Research Ethics and Bio safety Committee have approved the performance of this research work with reference no. as D/2298/MMG.

**Collection of samples:** Samples were collected from the Jinnah Hospital Lahore. Each 200 diabetic and cancer patients were selected. Information of the patient's past, present and socio-economic history was obtained. All ethical groups were included in the selection criteria. Population should be both male and female. Patient should have the symptoms of diabetes and cancer of various types. Pregnant females, lactating women, people who take any supplements of vitamin, major surgery and operations and Hepatitis etc were among the exclusion criteria. Consent was taken from each patient (Table 1).

**Physical parameters estimation:** Age of all the 500 subjects that consists of 100 controls, 200 diabetic and 200 cancer patients were calculated from the history of the subjects in years. Weight and Height of all the subjects were measured and then recorded in kilograms and inches (Table 2). BMI is

checked by dividing the weight of body with the square of the height (kg/m2). According to World Health Organization, the normal BMI ranges from 18.5 to24.9 and people with a BMI of 25–30 are overweight, while those with a BMI of more than 30 are obese. BMI is generally used to classify underweight, overweight and obese people.

Table 1: Number and percentages of different types of cancer.

| Cancer type | Total n=200 | Males(n=100) | Females(n=100) | Percentage |
|---|---|---|---|---|
| AML | 100 | 60 | 40 | 50% |
| Breast | 32 | 0 | 32 | 16% |
| Liver | 32 | 19 | 13 | 16% |
| Colorectal | 16 | 9 | 7 | 8% |
| Pancreatic | 12 | 7 | 5 | 6% |
| Lung | 8 | 5 | 3 | 4% |

Table 2: Average values of different parameters of control as compared to diabetic and cancer patients from Lahore population.

| Parameters | Control(N=100) | Diabetic (N=200) | Cancer (N=200) |
|---|---|---|---|
| Age (Years) | 50.8±1.30 | 63.33***±2.02 | 54.87***±1.58 |
| Height (m) | 1.66±2.12 | 1.67**±0.08 | 1.685**±0.10 |
| Weight (kg) | 60.5±1.2 | 67.9***±1.63 | 69.47***±1.80 |
| BMI (kg/m$^2$) | 25.4±0.40 | 27.45***±0.51 | 27.71***±0.57 |
| HbA1c (%) | 6.5±0.10 | 9.83***±0.24 | 8.39***±0.16 |
| BSF (mg/dL) | 95.32±8.78 | 188.73***±13.86 | 146.15***±10.66 |
| Bilirubin (mg/dL) | 0.71±0.02 | 0.60**±0.007 | 1.19***±0.17 |
| ALP(U/L) | 103.3±1.25 | 213.73***±1.34 | 108.1***±1.73 |
| ALT(U/L) | 42.04±4.56 | 44.63***±6.01 | 28.97**±1.97 |
| Creatinine (mg/dL) | 1.0±0.30 | 0.88**±0.22 | 0.78**±0.09 |
| Uric acid (mg/dL) | 4.9±0.40 | 5.77***±0.80 | 2.90**±0.16 |
| Serum Protein (g/dl) | 7.15±1.01 | 8.23***±2.48 | 8.02***±2.05 |

+sign indicates stand error. *=p>0.05 (non-significant), **=p<0.01 (statistically significant), ***=p<0.001 (highly significant) comparison of control with diabetic and cancer. Group 1 is control; group 2 contains diabetic patients while group 3 consists of cancer patients. Number of "*" asterisks show the level of different significance.

**Biochemical parameters estimation:**

**Protein assessment:** Measuring the quantity of protein is really important and an accurate estimate of the protein content is a vibrant step in protein assessment. Bradford assay is used to determine the amount of protein in sample. The quantity of Coomassie dye ligands binding protein molecule is proportional to the amount of positive charges present on protein. The Bradford reagent is made up of methanol and phosphoric acid that has Brilliant Blue G-250 (sigma Aldrich) in it. (Figure 1).

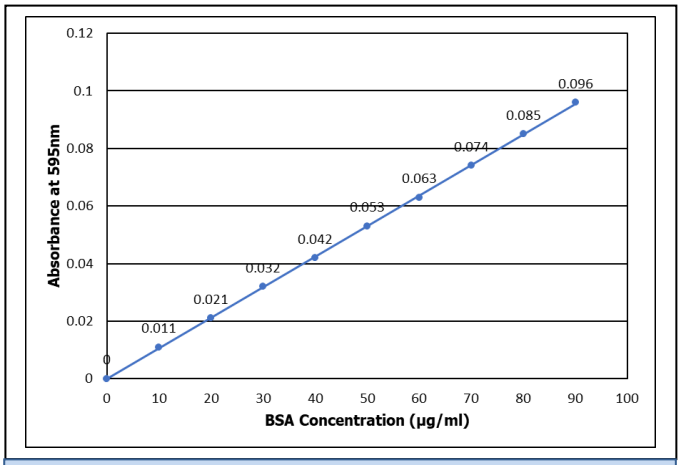


Figure 1: Graph shows the standard protein estimation by Bradford method.

**Procedure of Bradford assay:** (for sample with 0 to 90 µg/ml protein) 1 mg/ml BSA stock solution and 8-10 dilutions of standard BSA protein with a range of 0 to 90 µg/ml with an O.D range between 0.000 and 0.096 were prepared. Dilute unknown protein samples to get 10 to 90 µg protein/ml. Protein solutions are usually assayed in duplicate or triplicate. In 99 µl of water, 1 µl of sample was added to obtain an ultimate ratio of 1:100. 3ml Bradford Reagent was added to each tube. Place in incubator for 30-45minutesat 37°. Absorbance will enhance with time so samples should be incubated for less than an hour as protein dye complex is stable only for 1 hour. Transfer liquid into glass cuvettes to measure the absorbance at 595 nm [18].

**Glucose determination:** Glucometer was used for measuring Blood Sugar Fasting (BSF). The subject finger was sterilized with ethyl alcohol, a clean bulb syringe was used to rupture the skin, and blood drop on strip was taken and the reading was recorded. Standard curve was computed by O.D of reference against sample and protein (µg) in sample was calculated through formula i.e. (volume / length).

**Estimation of Blood Glucose:** Colorimetric with test strips 10mg/l Glucose MQuant® (MerckMillipore) was used to



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analyze glucose level. It is an in vitro diagnostic test for quantitative estimation of glucose in serum, plasma, urine and fluid.

**Determination of HbA1c:** Enzyme-linked Immunosorbent Assay Kit was used to estimate HbA1c in serum. HbA1c measures blood sugar level, which is used to determine if a person is diabetic or at risk of developing it. Reagents, samples and standards were prepared. 100ul standard or sample was added to each well and incubated for 2 hours at 37°C. Then aspirated and 100ul prepared Detection Reagent A was added and incubated for 1 hour at 37°C. Aspirated and washed 3 times. After that added 100ul of prepared Detection Reagent B and incubated for 30 minutes at 37°C. Aspirated and washed 5 times. Added 90ul substrate solution. At room temperature incubated for almost half an hour. At last added 50ul stop solution and read at 45nm without delay.

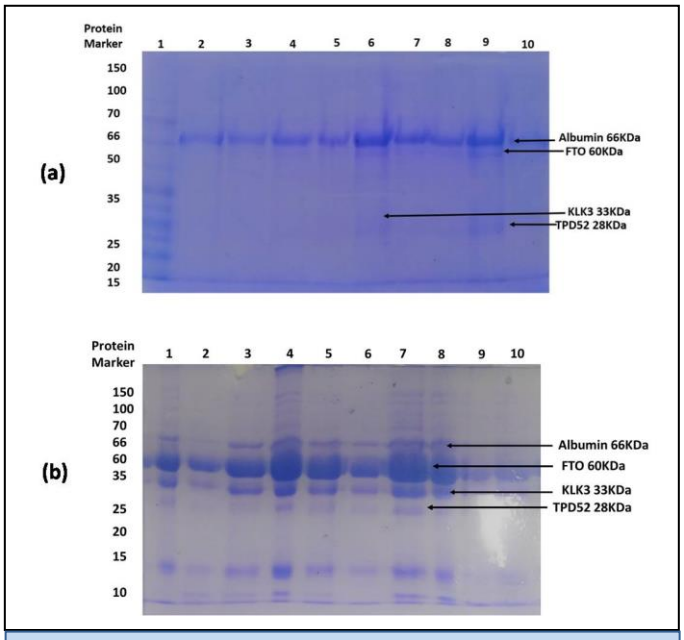


Figure 2: SDS page was performed in Research Lab I of MMG. Results of serum samples of diabetic and cancer patients. (a)First Lane: 150kDa protein marker (ladder), Lane 2-5: serum samples of diabetic and Lane 6-10: serum samples of cancer individuals. (b)Lane 1, 2, 6,9,10 contain serum samples of diabetic and Lane 3, 4,5,7,8 comprise of serum samples of cancer individuals. Figure demonstrates that bands in diabetic patients is in low concentration and was less expressed while bands of serum sample of cancer is present in high concentration and were highly expressed.

**Protein Analysis by SDS-PAGE:** The technique provided by [19] was used. Clean glass plates by washing and dry them. Assemble the glass plates with spacers and seal the bottom with tape. Prepare and pour the gel solutions. Resolving gel was poured in the gel assembly, leaving an empty space of 0.5 inches on top. Then stacking gel was put on top after polymerization of the resolving gel. Comb was incorporated into the gel to form wells for the loading of samples. Remove the comb, add buffer in electrophoresis tank and load sample in wells. A voltage of 120 V was set and after running, the gel was cautiously separated from gel plates and stained in Coomassie's brilliant blue stain for 30 minutes. De-Staining (concentrated methanol: acetic acid) solution was poured and left overnight until the clear bands appeared. Distilled water was added and rinsed with mild shaking for 5 minutes. Gel wrapped with a sheet of what man filter paper was dried at 60 ° C for 1 hour on gel dryer and viewed on illuminator (Figure 2).

**High performance liquid chromatography (HPLC):** HPLC is used to ascertain the existence of tiny quantity of a compound in any solvent and is based on the adsorption technique. Certain specific samples, after dilution were run on HPLC to confirm results of SDS-PAGE. TPD52 AND FTO assessment was done by HPLC (Model 203; Sykam, Eresing, Germany). At 5, 10 and 15 µl/l, standard solution (Sigma Aldrich > 97 percent) were prepared. Frozen samples at-80°Cwere defrosted to 20°C and reduced to 10µl/l. Samples were processed with nylon syringe filters of 0.2 µm. They were then loaded into eppendorf. BSA standards were developed in concentrations of10 µg/l and 15 µg/l of protein and then purified using syringe filters. 200 µl methanol, 50 µl of sample and standards were placed in an eppendorf and analyzed by HPLC. ODS C18 column of hypersil-keyston (5 µm; 4.6 upper 250 nm) was fitted. Methanol/water/acetic acid (36:64:1) was the portable solvent at 1ml /minute rate. At 220nm elutes were identified and TPD52 & FTO were spotted. Samples were inserted into sample loop at atmospheric pressure from the syringe, later connected with solvent flow. Introduced pump that brought serum samples to columns of C18. Results of sample from the display monitor were generated through program (DATA APEX: Clarity Chromatography Station) and recorded after the specific time period (Figure 3).

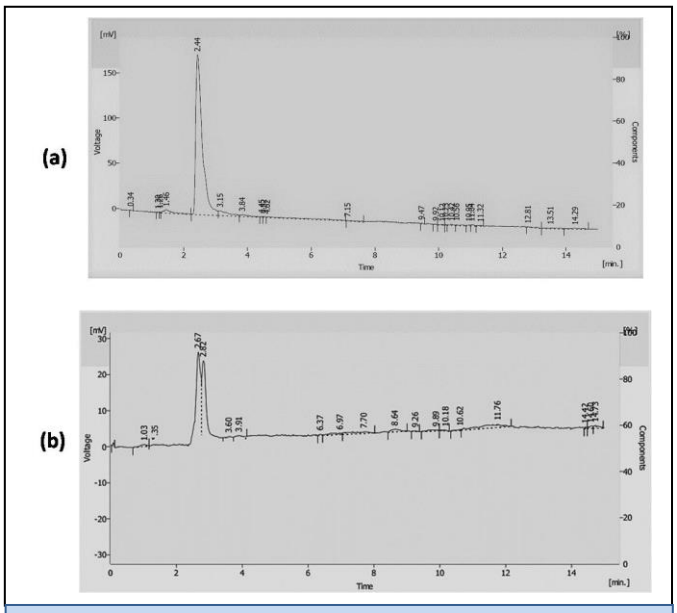


Figure 3: (a,b) HPLC Chromatograph showing peaks for TPD52 and FTO with standard peak run alongside. Some small peaks are also observed due to impurities or handling errors.

## STATISTICAL ANALYSIS

The research objectives were checked in all participants with study group size of N=500. All other variables were analyzed and statistical analysis was done with SPSS statistical software package of version 22.0. Significance of difference between mean analysis of control, diabetics and cancer patients was determined by applying one sample T- test. Collectively 400 patients suffering from Diabetes Mellitus and cancers (lung, pancreatic, breast, colorectal, liver and acute myeloid leukemia) i.e. 100 Males, 100 Females suffering from diabetes and 100 Males, 100 Females having cancer along with 100 healthy controls were included in the research. The data was first analyzed in Microsoft Excel for finding the means, standard deviation and standard error. Graphs were also generated using Microsoft Excel. One sample T- test was performed using IBM SPSS. The variables of healthy control subjects, people with diabetes mellitus and different types of cancer were compared by applying paired T-test.

## RESULTS

In study three study groups were formed and the samples were first analyzed for the physical parameters: Age, weight, height and BMI of all individuals. Normal control individuals were grouped in Group 1, diabetic male & females in Group 2 and cancer males & females in Group 3. Biochemical parameters like total protein assessment, bilirubin, create nine, HbA1c levels were estimated. Of the 500 participants, 200 were diabetic from Lahore, 200 were cancer patients and 100 were control healthy individuals. Among the physical parameters, age, weight, height and BMI showed results that were statistically significant. HbA1c, total serum protein, create nine, urea and bilirubin of the diabetics and cancer individuals was greater as compared to healthy individuals. The results showed that value of blood fasting sugar contents in diabetic and cancer patients was increased as compared to the healthy controls (Figure 4). The level of protein is higher as compared to the normal people. The mean value of protein in diabetic cases was 8.23±2.48g/dl, in cancer individuals it was 8.02±2.05g/dl and in controls the mean value was 7.15±1.01 g/dl. The results show statistically high level of protein in diabetics and cancer patients as compared to the control group with $p<0.001$. Albumin protein (66KD), TPD52 (28KD) and FTO (60KD) were found by SDS-PAGE analysis. The results of Bradford test also demonstrated increased level in the diabetic and cancer as compared to the healthy group. Comparison of physical and biochemical parameters of control, diabetic and cancer male and female patients is shown in (Table 2).

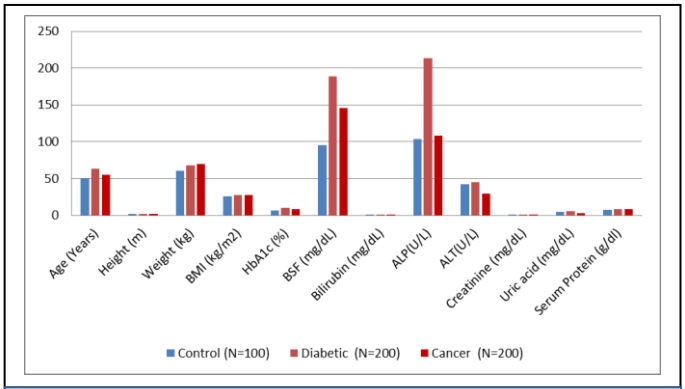


Figure 4: Graph between average of physical parameters (Age, weight, height, BMI) and biochemical parameters (HbA1c, Blood Sugar Fasting, bilirubin, ALP, ALT, creatinine, uric acid and protein, of control, diabetic and cancer patients of Lahore.

## DISCUSSION

In this study total 500 subjects were selected and were classified in 3 groups. First group was control, second was diabetic male and female and third group included cancer male and female patients. Various physical and biochemical



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parameters were accomplished to assess the difference between the two populations and the controls. First physical parameters (age, weight, height & BMI) of diabetes and cancer individuals were recorded. A comparison regarding these parameters with normal healthy control subjects found increase in the mean value of patients suffering from different types of cancer and diabetes. The BMI in diabetics and cancer patients was higher from normal healthy control subjects. It was also revealed that a raised BMI value is related to a higher chance of diabetes and cancer. Biochemical parameters were assessed including blood sugar fasting, HbA1c, renal function tests, liver function tests and total serum protein estimation. The patients of diabetes having high HbA1c level are more prone to develop micro vascular and macro vascular disorders [20]. A significantly raised level of blood fasting sugar in diabetics, and cancer patients was noted ($P< 0.001$). Chronic hyperglycemia, quantified by HbA1c, corresponds to greater risk of colorectal, lung, liver, pancreatic, and breast cancer [21]. Descriptive statistics found that postoperative tumor recurrence in diabetic patients was associated with poor glycemic control (HbA1c≥6.5 percent) and chance of Hepatocellular Carcinoma (HCC) increases with greater HbA1c level [22]. Uric acid is an important risk factor causing diabetes mellitus [23]. The level of uric acid in diabetic patients under consideration was significantly higher than in cancer individuals. The result of total serum protein was statistically significant ($P<0.001$) means that protein level of patients suffering from diabetes and cancer was higher than that of normal control subjects. Bradford test is used to calculate the concentration of proteins in micro levels in serum of all diabetic and cancer subjects as compared to normal healthy control subjects which revealed a substantial increased level of proteins. A significant difference was observed when serum protein bands of patients were analyzed on SDS PAGE gel. The bands resulting from the serum of patients suffering from diabetes and cancer were large, huge and clearer. Main target proteins FTO (60 KDa) and TPD52 (28KDa) were observed in diabetic and cancer individuals. Albumin proteins constitute 50-60% of total proteins found in body. It has 66.7 KDa molecular weight [24]. A high value of albumin protein is considered to be related to the final stage of kidney disease. It can be treated by amino acid supplementation [25]. The consumption of protein rich diet as compared to carbohydrates and fat increases risk of diabetes and cancer whereas the habit of taking cereals and fiber rich food can control it [26]. Consequently, cancer incidence in diabetic and non-diabetic populations may theoretically be decreased by lowering levels of glucose. This could be accomplished by suitable lifestyle or clinical measures and through strict glycaemic regulation guidelines [27].

## CONCLUSION

The problem of obesity is a major issue and is very closely related to diabetes which itself is expanding leading to cancer risk. It can be minimized by controlling the BMI to safer limits in individuals who are unaware of its consequences and don't take proper check and balance of their eating habits, diet and routine activities. Diabetes and cancer patients may develop many other complications that increase their suffering. It is important to take preventive measures in order to combat diseases. These measures include body mass index, sugar level, HbA1c, uric acid, creatinine, bilirubin and serum proteins. BMI, when increased, disrupts the body function and can lead to Diabetes Mellitus, which is a risk factor for cancer so, it should be maintained to a normal range both in patients suffering from Diabetes Mellitus and cancer individuals. An increase in blood sugar level results in the disturbance of the metabolic system of body. All the other parameter studied should be maintained to a normal range. By taking these preventive measures, diabetes and different types of cancer can be controlled and can be less dangerous.

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## CONFLICT OF INTEREST

The author(s) declare that the publication of this article has no conflict of interest.

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