Review Article

Estimation of Serum Creatinine in Type 2 Diabetes Mellitus Patients and Linked Renal Anemia Risks

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Abstract

Diabetes mellitus is a metabolic disease affecting blood glucose homeostasis in which its levels raises out of the normal range. As the time goes on, diabetes comes with different complications following physiological alterations damaging body organs and structures. At the kidney level, this disease interfere with wastes removal and erythropoietin production resulting in anemia. Serum creatinine estimation is performed to assess renal insufficiency to care for diabetic patients' kidney health. Diabetic patients with uncontrolled blood glucose attending Gee Bee Hospital, were enrolled in this study alongside with patients having neither diabetic nor renal issues history used as control. Blood samples taken from all of them were analyzed for CBC and serum creatinine level. Among 36 patients, 30.6% were reported with both abnormal high serum creatinine and anemia most prevalently in elderly patients compared to young ones, for only one person in young group was with high serum creatinine. In addition, other patients with normal creatinine level were also reported to be anemic making a total of 63.9%. Mild anemia was prevalent followed by moderate anemia. Blood indices analysis showed that normocytic normochromic and microcytic hypochromic cells were dominant with equal percentage. Serum creatinine level in Type 2 Diabetes Mellitus (T2DM) patients having uncontrolled blood sugar was found to be high. This gives an information about renal insufficiency of the patients leading to the loss of erythropoietin thus increased rate of anemia.

Keywords: Serum creatinine; Diabetes Mellitus; Renal insufficiency; Hematological parameters; Diabetic nephropathy

Introduction

Definition and types of diabetes mellitus

Polycystic Diabetes Mellitus (DM) is referred to an increased level of glucose in the blood (hyperglycemia) due to imbalance in either production or efficacy of insulin from beta cells of the pancreas without efficient treatment to such high concentration or Insulin Resistance (IR) by muscle cells [1]. This metabolic disease is globally classified into two main types: Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). T1DM is characterised by absolute or almost absolute inability of pancreas to produce insulin caused by auto antibodies that attack beta cells of the pancreas, notably insulin tyrosine phosphatases and glutamic acid decarboxylases reducing or leading to absolute lack of insulin, an anabolic hormone that plays a role of reducing glucose from the blood. This type is most common in young people but also few cases were reported from mature people of any age. On the other hand, T2DM is described as diabetes in which the body does not respond to the produced insulin as required, referred to IR [1,2]. A group of people vulnerable to this type of diabetes include those from family having diabetes history, people with increased age, obesity, women having history of pregnancy diabetes and sedentary lifestyle, physical inactivity, inappropriate meal and hypertension, the risks that may be montained if the health style are improved [3,4].

Alongside these two most common DM types there some others to know; Gestational Diaberes Mellitus (GDM) and Mature Onset Diabetes of the Young (MODY). GDM is any glucose intoleerance or DM condition reported during second or third term of the pregnancy. This type of DM affects around one to fourteen percent of all pregnancies. Maturity onset diabetes of the young is another types of diabetes mellitus caused by a genetic mutations in the genes responsible of functionalityt of islet beta cells. This results in glucose sensing failure and hence inability of producing insulin though when produced with MODY condition is a normal or minimally defected insulin. MODY is confused with T1DM in clinics because of its early onset, below 25 years old, but it is actually a non-insulin dependent disease differs from T2DM by its genetic pathogenesis [5].

Common symptoms and complications of diabetes mellitus

Both of these two types have some symptoms in common though some diffeences may also be identified. In case of diabetes mellitus, the affected person presents frequent urination (polyuria) caused by the dilution of glucose excreted within urine, followed by a higher water uptake (polydipsia), increased hunger, frequent eating (polyphagia). The common difference sign between the two types is the development of ketoacidosis (as alternative source of energy) in type 1 diabetes which is not developed in type 2 for a lttle amount of insulin is produced in the patients with this type [6].

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Diabetes Mellitus is associated with, time-dependent complications that affect different organs of the human body. These biochemical changes are driven by the glycation of protein components of the system ranging frrom hemoglobin, apolipoproteins to cell membrane bound receptors. Further oxidation and rearrangements of such glycated proteins result in highly active species known as Advanced Glycation End product (AGE). AGE are recognised and accepted by their corresponding receptors on endothelial cells. This binding induces a chronic low grade immune response that ends in complications of diabetes mellitus [7]. The complications caused by different metabolical changes in diabetes mellitus are grouped into two categories which are microvascular and macrovascular complications. Microvascular involves the damage to the neurones (neuropathy), effects to kidney nephrons (nephropathy) and damage to the cells of the retina (retinopathy). It also affects large peripheral vessels causing complication like artherosclerosis, stroke and heart attack commonly reffered to macrovascular complications of diabetes mellitus, sight problems, delayed wound healling, vulnerability to infections (fungal infection mostly) and increased risks of dementia, in which the memory is affected [8,9].

Some of the complications are treatable and recover imediately despite their episodic repetition, but others are progressive instead. For example, nephropathy progresses with time from mildy damage up to renal failure, the level at which the kidney damage is irreversible. Diabetic Nephropathy (DN) is defined as the passing out of proteins in urine reaching 500 mg of proteins or 300 mg of albumins per day from the patient having no any other disease that may cause proteinuria or albuminuria apart from diabetess mellitus. Diabetic nephropathy reveals faster within patients with T2DM than T1DM and its onset is predicted after 10 to 15 years after the onset of diabetes [8,6].

Renal function is estimated routinely to follow up and monitor the effects of a certain diseases to the kidney [10]. Estimated glomerular filtration rate was performed using inulin to estimate renal function but due to time consumption it has been replaced by creatinine whose clearancefrom the blood by glomerus indicates the ability of the kidney to remove metabolic wastes from the blood and its level of damage in chronic diseases conditions. Morever, urea, electrolytes (sodium, potassium, calcium chloride) and uric acid are used to check up the kideny functions though estimation of the serum creatinine in diabetic patients is mostly performed for early diagnosis of acute or chronic renal disease, the conditions that may interfere with the production of erythropoietin, a hormone that normally acts on borne marrow to produce red blood cells, thus its production impairment may results into anaemia [11-14].

Epidemiology of diabetes mellitus

Morbidity caused by diabetes mellitus and its complications is affecting many people around the globe, this ranks such a noncommunicable disease the nineth among ten leading high mortality causing diseases worldwide in the year 2019 [15]. Few years back, 2013, it was reported that people with diabetes were estimated to be 382 million and expected to drammatically raise up to 592 million of people by the year 2035. The report showed that India was ranked the second after China to have a huge number of DM patients aged between twenty and seventy nine [16]. Also according to the International Diabetes Federation, India remained on the same ranking position in 2019 and it is estimated to stay so in 2045, the year in which diabetic patients will approximately be 134.2 million from 77.0 million in 2019 [17]. A big challenge to health care partitioners is that a multitude of individuals won't be aware of their health burden, undiagnosed, the situation which will worsen both morbidity and mortality caused by diabetes [18].

Developing countries including India are mostly threatened with this increasing prevalence of diabetes mellitus. The study done by Indian Council of Medical Research (ICRM)–India diabetes in different states of India revealed that urban population are more affected than people living in rural areas. This is in regard of both diabetic and pre-diabetic (impaired glucose tolerance). Same study reported that the prevalence of DM was 12.0% and 8.7% in urban and rural areas resspectively in Punjab state. The rate of pre-diabtetic prevalence in the same state was estimated at 8.6% in urban place and 7.9% in rural areas [19]. The fact that Asian Indians are among the groups of people with high risks of developping diabetes, high mortalitty linked with diabetes and its complication, increased prevalence of pre-diabetetic and estimated increase in diabetes mellitus prevalence raise the emergency of this disease in India parrticulary [19,20].

Objectives and need of the study

By estimating serum creatinine, the renal function in DM patients is assessed and the risk to develop renal anaemia maybe analysed to reveal at which extent this type of anemia is prevalent in DM patients. This information is helpful to both patients and medical care partitioners and local health policy makers to take care of DM management. People with DM need to go for early treatment to avaoid early complications linked with this health threatening meatabolic disease. On the other hand, local health partitioners need the accurate inforation about the epidemiology of renal function in people with DM. This study is a good opportunity and referencee to boost the sensitization and motivate health policy makers aiiming on looking after and inprove the health of their population, even preventing new cases of DM and/or its linked complcations as much as possible. The objectives of this study include:

- Estimating serum creatinine in T2DM patients with uncontrolled blood sugar.
- Correlating the impaired renal function in T2DM patients with the age.
- Assessing the prevalence of anemia within such a group of people.
- Correlating the anemic condition with serum creatinine and sugar levels.

Literature Review

Pathophysiology of type 2 diabetes mellitus

This is the type of diabetes which does not depend on insulin (non-insulin depend type of diabetes) and it is mature onset. The most vulnerable population to this type include these with

unusual obesity, age, diabetic family history, having gestational diabetes. People with hypertension and dyslipidemia (in which high density lipoproteins are very low) are at high risk which explains why T2DM patients also suffer from cardiovascular diseases frequently. In all these conditions, the patients suffer from either insulin resistance or decreased insulin production resulting in hyperglycemia whose mismanagement leads to asymptotic development of diabetes mellitus in early stages of a disease [5].

Mechanism of insulin production and secretion

Islets of Langerhans have a function of producing insulin that is in turn responsible of moving glucose from the blood circulation into the cell for energy production. According to Galicia-Garcia et al., this insulin is firstly produced in pre-proinsulin form which is also processed by specialized proteins located in Endoplasmic Reticulum (ER) to yield to a proinsulin [21]. Proinsulin is packed into vesicles then transported to Golgi apparatus where it is cleaved to release C-peptide. Mature insulin is at this time stored in granules ready to be release following the increased level of glucose mainly, but also amino acids, fatty acids and change in hormonal circulation. For pancreas to fulfil its functions, it needs Glucose Transporter 2 (GLUT 2) which takes in glucose. The metabolism of pumped in glucose molecules generates a huge energy inside the pancreatic cells. This increase in ATP mediates two scenarios which lead to the secretion of insulin: Closure of ATP dependent potassium channels and calcium pumps activation to allow calcium entering the cells. Calcium ions inside the cell induce the fusion of insulin containing granules and cytoplasmic membrane thus its excretion. Beside this normal mechanism, it was also reported that insulin excretion is enhanced by other signals mainly cAMP (cyclic Adenosine Monophosphate) that increases calcium concentration inside the cell by acting on intracellular calcium storage [22].

Compromised insulin exocytosis and DM pathogenesis

The mechanism described above is affected by abnormal high glucose and lipid levels in the blood which leads to the loss of β-cells integrity thus the loss of its functionality regarding insulin anabolism and secretion. This disruption of β-cells integrity is mediated by oxidative stress to β-cells ER and resulting inflammatory response caused by the impaired homeostasis of these two nutrients. The stress caused by saturated free fatty acids has the potentiality of inhibiting SERCA, (responsible for calcium ions secretion of ER mobilization) or by direct effects on ER causing decreased production of insulin. On the other side, high glucose is busy causing the production and accumulation of proinsulin and Islet Amyloid Polypeptides (IAAP). A continuous buildup of these two products ends in the production of Reactive Oxygen Species (ROS). In such conditions normal and healthy ER signaling pathways are compromised, proinsulin mRNA is precociously degraded without producing insulin and Il-1 mediated inflammation enhances the immune response against β-cells [21].

Role of insulin resistance in T2DM pathogenesis

The functions of insulin are affected by body mass index out of range. Whenever BMI is greater than 25, a value taken as upper reference limit to report a person as obese, following high fat containing foods intake, refined (processed) sugar based foods consumption and sedentary lifestyle accompanied with insufficient physical activities, a person is at increased obesity risks. This obesity subjects the body to insulin resistance (loss of insulin capability to signal its target cells) and results in impaired fasting glucose and impaired glucose tolerance which further progress into T2DM. At the level of skeletal muscles, IR disrupts the functions of GLUT 4, glycogen synthase and hexokinase which plays an important role in peripheral glycogenesis, thus the reduced glucose storage rate inside myocytes. To this myocytes glucose intake failure, the liver adds its gluconeogenesis and glucogenolysis products (additional glucose) that keep on raising circulating glucose. This resistance changes biological mechanisms which leads to hyperinsulinemia, dyslipidemia, hyperglycemia and increased blood pressure which are detectable in T2DM and pre-diabetic patients [23].

Advanced glycation end products and T2DM

Red blood cells, vascular endothelial cells and mesangial cells of the kidneys are among the cells of human body which express a high amount of GLUT1. To such cells hyperglycemia management becomes a heavy burden and the condition becomes worse in case of mesangial cells which overexpress such a type of transporter compared to other types of cells [24]. Among the physiological changes following this elevated glycaemia in such cells, the formation of AGEs is the most known. AGEs involves the reaction between glucose and plasma proteins and structural proteins (collagen, albumin, fibrinogen and globulin) and their formation is directly linked with retinopathy, neuropathy and nephropathy as diabetes mellitus complications. The development and accumulation of AGEs inside the cell alters normal cell physiological functions which end up in formation of generation of free radicals, autoimmune generation, decreased glucose intake, inflammation, atherosclerosis development and many other health threatening conditions leading to the morbidity of T2DM patients [25].

AGEs are formed from the reaction involving carboxyl group of glucose and/or any other reducing sugar with amino group of involved protein. In early stage of the reaction Schiff base which is instable (having the capability of reversing to give back reducing sugar and proteins that caused its production) or progress to Amadori product which is more stable than Schiff base. Amadori product undergoes chemical degradation driven by its oxidation or loss of water molecule (dehydration) to produce different compounds known as oxoaldehydes in intermediate stage. From this stage, the generated compounds progress to late and final stage of the mechanism that forms AGEs [25].

AGEs and nephropathy

The expression of receptors for AGEs on the surfaces of the cells like endothelial cells, macrophages and the cells of smooth muscles plays a big role in DM complications by mediating the alteration of cells functional proteins through transducing the message coded by these AGEs. The number of Receptor for AGE (RAGE) increases in diabetic patients that explains

why DM patients are subjected to complications, but also the inflammation elevates the number of RAGE expressed on the cell membrane, in such a situation, they will transduce the message brought by inflammatory cytokines [25].

The study done to investigate the role played by the interaction of AGEs and RAGE revealed that the suppression of RAGE expression improves DM linked nephropathy [26]. The interaction between AGEs and RAGE generates ADMA (asymmetric dimethylarginine) at the level of tubular cells. Finally ADMA inhibits nitric oxide synthase. Such physiological alteration modifies tubular cells functions and advances the patients to renal complications, its inhibition was reported to delay diabetic nephropathy [27]. In addition to this, AGEs are also linked with the damage of DNA in podocytes and the uncontrolled accumulation of extracellular matrix proteins around mesangial cells, this results in much collagen in ECM. Glycated collagen mediates local structural degradation by interacting with other biomolecules and thus the loss of physiological functions of tubular cells [25,28]. Alongside AGEs damages to the kidney cells, other signaling pathways were reported to play their important role in the development of nephropathy in diabetic patients. This includes oxidative stress mediated by ROS that maybe produced through polyol pathways, but also by AGE. This oxidative stress also progresses to local or systemic inflammation by different inflammatory cytokines like Il-1, 6 and 18, TNF-α which are powerful agents of diabetic nephropathy pathogenesis characterized by proteinuria and tubular fibrosis. Such a fibrotic state of the kidney is due to prolonged hyperglycemia inducing oxidative stress which acts on the levels of Angiotensin 2 whose increased levels activates the release of transforming growth factor β. Both Angiotensin 2 and TGF-β were also reported to be among the reasons behind the alteration of ECM of mesangial cells [29].

The development of this DN subjects the body to the leaking of EPO and transferrin in urine. The pass out of these two essential components of erythropoiesis causes a reduced blood cells production, for there will be no enough EPO to signal bone marrow for erythropoiesis and degradation of transferrin molecules cause EPO and iron deficiency type of anemia [30].

Materials and Methods

This was a kind of cross section study conducted on blood samples taken from T2DM patients attending Gee Bee hospital and maternity home for routine checkup. Gee Bee hospital and maternity home is a private hospital located in Phagwara, a city in Punjab state of India. From 01 February, 2023 to 31 March, 2023 thirty six participants were considered for this study and ten participants free from diabetes mellitus, renal diseases or any other condition that would raise up serum creatinine out of the normal range were taken as controls. For all these samples, serum creatinine was estimated using erba EM 200 biochemistry analyzer and erba hematology analyzer was used for the complete blood count from which red blood cells indices were taken into consideration.

The sample collected from all participants were processed through two pathways: The blood samples for CBC test were collected in EDTA tubes (vials with purple caps) to avoid early and unpredicted clotting of the blood. Same samples were then mixed using hematology mixer prior to load into erba hematology analyzer H 360 for the complete blood count. On the other hand, the samples for biochemical analysis (estimation of creatinine), were collected in clot activating vials with red caps, centrifuged at 1500 rpm for five minutes then analyzed by erba biochemical analyzer (erba EM 200).

After the laboratory work, the collected data was arranged and analyzed using Microsoft excel 2013. By the help of student T test, the data was analyzed for difference in statistical parameters whenever required. The tolerable error of 5% (0.05) was taken for this study.

Results

General characteristics of the group

Thirty six patients with poorly controlled blood sugar were enrolled in this study. The average age of the group was 62.68 years and a standard deviation of the mean of 10.68 years. 21 of the total participants were females representing 58.3% of the study group and the remaining 15 were males with 41.6%. The studied group was subdivided into two age groups (Table 1).

The table that follows summarizes the means and corresponding standard deviation of analyzed parameters across the DM type 2 patients and control samples. The reference ranges and the units for each parameter are also mentioned in the Table 2.

According to student T-test the difference mean value between Random Blood Sugar (RBS) of DM patients is significant, however, the test proved that the difference in the mean of other parameters (that is Hb, RBC, PCV, MCV, CRT) is not significant. None of the parameters was reported significant between male DM patients and female DM patients.

Assessment of serum creatinine and associated risks of anemia

Serum creatinine level was estimated between the range of 0.6 mg/dl-1.10 mg/dl and 0.7 mg/dl-1.30 mg/dl in females and males respectively. Eleven patients, 30.6%, were found with impaired serum creatinine levels, among which 10 participants were aged above 60 years old and only one patient was below 60. Five of them were males and remaining 6 were females. The prevalence of anemia within the studied group was found to be at the rate of 63.9%. In addition to 11 patients with impaired serum creatinine, there were also other 12 patients who were anemic before manifesting increased levels of creatinine to give a total of 23. Females and old participants were more vulnerable to anemia (Figure 1).

Mild anemia was dominant over moderate anemia by 73.9% to 26.1% of the total anemic patients respectively. According to the red blood cells indices, four types of cells were noticed referring to the reference ranges of MCV and MCH (Table 3).

Blood cells indices of anemic patients were compared to control samples and no significance variation in their mean was noticed.

Table 1: Age characteristics of study group.

Age group	Females	Males	Total
<60	2	8	10
≥ 60	13	13	26
Total	15	21	36

Table 2: The reference ranges and the units for each parameter.

Parameters	Reference range	Control	Test	Females	Males
Age	years	49.1 ± 17.19	64.4 ± 10.5	63.3 ± 11.3	66 ± 8.6
Hb	12.0 g/dl-18.0 g/dl	13.7 ± 1.1	11.6 ± 1.8	10.8 ± 1.4	12.7 ± 1.6
RBC	4.5 millions-5.5 millions	4.7 ± 0.3	4.3 ± 0.6	4.28 ± 0.5	4.5 ± 0.6
PCV	36%-45%	39.9 ± 4.1	35 ± 5.1	33 ± 4.2	37.76 ± 4.8
MCV	80 fl-100 fl	84.6 ± 5.9	80.3 ± 9	78.4 ± 7.7	82.9 ± 9.6
MCH	27 pg-31 pg	27.2 ± 1.4	26.5 ± 3.2	25.5 ± 2.9	28 ± 0.3
CRT	0.6 mg/dl-1.10 mg/dl in females and 0.7 mg/dlin-1.30 mg/dlin males	0.87 ± 0.15	1.13 ± 0.6	1.15 ± 0.79	1.11 ± 0.32
RBS	70 mg/dl-130 mg/dl	94.3 ± 10.7	203.6 ± 59.9	212.9 ± 60.1	190.5 ± 55.1

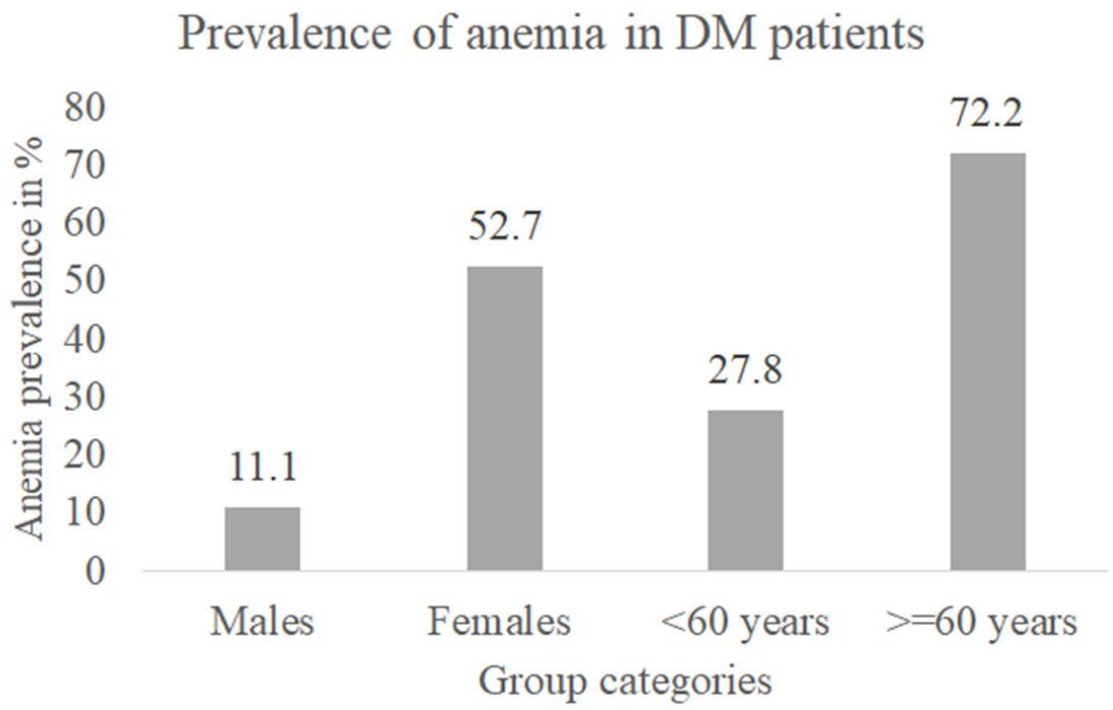

Figure 1. Prevalence of anemia in DM patients.

Table 3: Size of red blood cells and their frequencies.

Type of the cell	Frequency
Normocytic normochromic	43.40%
Microcytic hypochromic	43.40%
Normocytic hypochromic	8.60%
microcytic normochromic	4.30%

Hemoglobin, serum creatinine and serum glucose correlation

Impaired serum creatinine level was negatively correlated to the amount of hemoglobin estimated. This implies that as the creatinine levels increase hemoglobin decreases and this raises up the risks of developing anemia. However, the correlation was not strong enough as the correlation coefficient was below 0.5 (Figure 2).

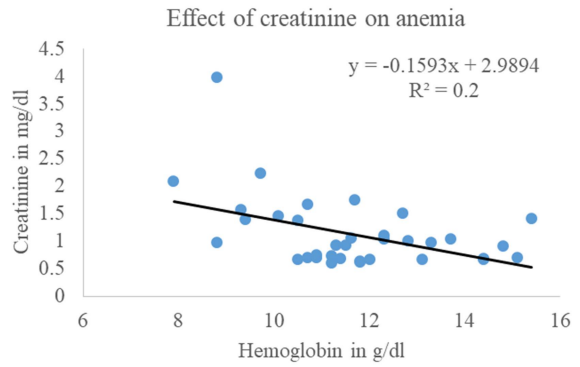

Figure 2. Correlation between creatinine and hemoglobin levels.

Almost similar results were observed for serum glucose levels. This parameter was also negatively correlated with the level of hemoglobin in the group. Beyond being negative, the correlation was also weaker than the one observed when creatinine level was compared to hemoglobin levels (Figure 3).

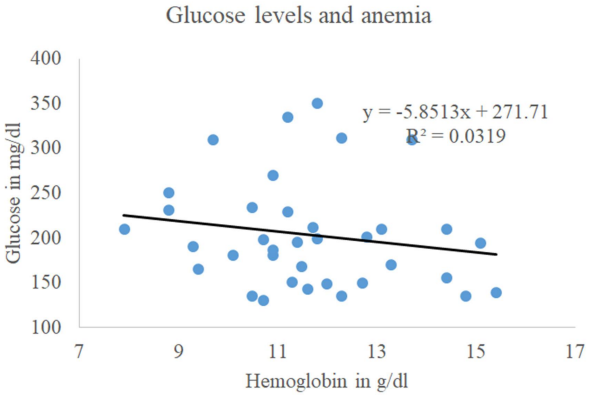

Figure 3. Correlation between serum glucose and hemoglobin.

Figure 4 below deduced from the mean values mentioned in Table 1, shows that hematological components analyzed in this study were slightly low in DM patients as compared to control group.

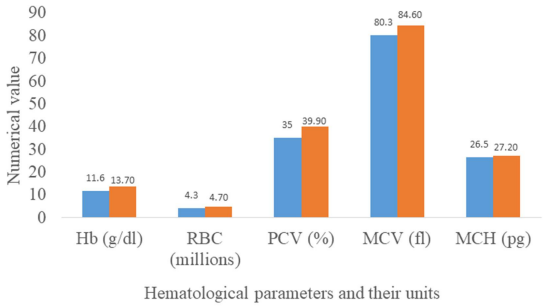

Figure 4. Correlation between serum glucose and hemoglobin. **Note:** (■) DM patients, (■) Control

In the same way, Figure 5 below indicates that females suffer more from anemia related issues due to DM than males though the different in mean values is not significant (slight difference).

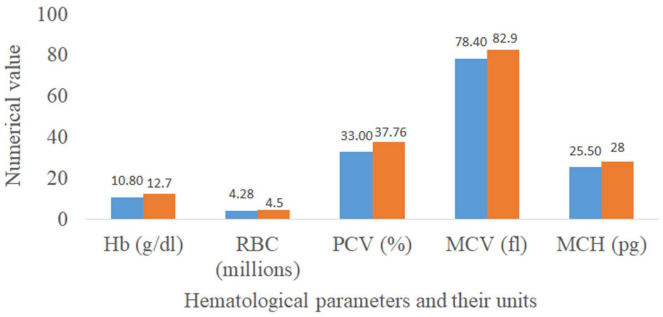

Figure 5. Comparison between males and females hematological parameters. **Note:** (■) Females, (■) Males

Discussion

As mentioned in the results above, the rate of impaired serum creatinine was found to be at the rate of 30.6%. The results close to this was also identified in the study done in Iraq where 10 participants among 30 were with raised serum creatinine [31]. On the other hand, a higher percentage was noted in the study carried out in Ethiopia, 43.2% with a higher number of impaired creatinine levels in adult patients [32]. The difference in outcomes might be due to different parameters which were not taken into account during the current study like social characteristics of the participants, use of alcohol, family history and disease severity and the duration of the study.

Anemia in studied group was with high percentage compared to the results found in other studies areas the globe, 63.9%. Compared to 20% and 20.1% found in Australia and Ethiopia respectively, this result is too high but close to 63% reported in Egypt and Pakistan [33-36]. This life threatening condition is more prevalent in patients with chronic kidney diseases and the condition worsens in DM type 2 patients for the present anemia earlier than ones with CKD only [37]. In renal dysfunction, anemia was linked to the downregulation of erythropoietin caused by the dropping down of hemoglobin level as reported by Deborah et al., [38]. As if this was't enough, a third of DM type 2 patients are under risks of developing anemia before the impairment of kidney functions [39]. This might be one of the reasons why anemia was prevalent in selected participants. In addition to this, the part of poorly controlled blood glucose level shouldn't be under looked as it was linked with elevated numbers anemic DM type 2 patients in Pakistan, in Kuwait, Benin and Nigeria [36,40,41]. This pre renal impairment in DM patients might be explained by inflammatory nature of DM type 2 that interfere with iron metabolism from its intestinal absorption to its circulation in blood through the production of hepcidin from the liver that mobilizes the storage of iron in bone marrow and inhibit its utilization by red blood precursor cells [42,43].

A great percentage of normocytic hypochromic cells was reported in the work done by Taderegew and the colleagues with a minimum frequency of microcytic hypochromic cells [34]. Though microcytic anemia is also linked with chronic diseases,

was reported to be high in the study done by Kaushik et al., [43]. in Haryana state of India, further studies might reveal the reason behind this increased percentage of microcytic hypochromic cells in local DM type 2 patients noticed in the current study, for better prognosis. Regarding the classification of anemia according to its severity, mild anemia was also reported higher than moderate anemia in the work done in Ethiopia [34].

Conclusion

This study approved the correlation between anemia and uncontrolled blood sugar in DM type 2 patients. Moreover, the patients without renal insufficient (impairment) were also reported to be at risks of anemia. Medical follow up is mostly required to the patients with this disorder, to control blood sugar the way that the development of prerenal impairment anemia will be delayed for it mentioned its potentialities to enhance both macrovascular and microvascular complications of DM type 2. In anemia with renal insufficiency, in which erythropoietin is dramatically decreased, a special care is needed to minimize the morbidity and mortality in such group of patients. Human recombinant erythropoietin has saved the lives of many having same complications.

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