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Assesment of serum taurine level as a potential biomarker for early diagnosis of diabetic nephropathy

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Abstract

Objective: Measuring of serum taurine as an early marker to detect and prevent complications of Diabetic nephropathy.

Method: Ninty diabetic patients (male and female) were chosen from Ahmed Maher hospital after their approval, eighty patients classified into four groups (diabetic control group, early stage group, before dialysis group, after dialysis group) according to its Complete clinical examination, investigation and biochemical analysis, twenty diabetic controlled patients not suffered from kidney impairment considered as diabetic control group. ten frank healthy non diabetic persons enrolled as volunteers. Complete clinical examination, investigation and biochemical analysis (liver and kidney functions, lipid profile), add to measuring Blood sugar, HbA1c, and the recent biomarker taurine, was measured for all patient and volunteers.

Results: The data showed non-significant change in lipid profile, creatinine in urine, and serum Albumine in all patients regarding to control group (P>0.05). that Liver function in all groups demonstrated non significance between groups,but values recorded significant changes in all groups of patients related to frank control group (p<0.05). Kidney function (urea – creatinine) values recorded very highly significant changes in all groups of patients related to frank control group (p<0.00), except controlled diabetic group and Early stage of diabetic nephropathy. also, there is a highly significant changes in blood glucose and HbA1c (P<0.001). On the other hand, the data showed extremely significant decrease in serum taurine in all diabetic patients according to the severity of diabetic nephropathy compared to that recorded in healthy control (P<0.000).

Conclusion: Serum taurine is reduced in diabetic patients with advanced conditions of diabetic nephropathy. Taurine Level is considered as an early marker (prognostic) to detect and prevent the diabetic nephropathy complications.

Keywords: Taurine; Diabetes mellitus; Nephropathy; Diabetic nephropathy; chronic kidney disease

1. Introduction

About ten percentage of the population suffers from diabetes mellitus, a serious public health issue. Pharmacotherapy seeks to prevent microvascular side effects such amputations, end-stage kidney disease, and blindness[1]. There are two types of diabetes mellitus: type 1 diabetes (T1D), which is characterised by a lifelong need for insulin therapy due to the loss of beta cells in the pancreatic islet as a result of an autoimmune reaction [2]. Most persons with type 1 diabetes struggle with hypoglycemia, weight gain, and a large amount of self-care because they are unable to achieve enough glycemic control to prevent complications. Promising pharmacological advances in insulin therapy include the

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development of highly fast insulin analogues, alternative insulin administration systems, liver-selective insulins, add-on medications that improve insulin effectiveness, and glucose-responsive insulin molecules [3]. Type 2 diabetes mellitus (T2DM), which affects about 25% of those over 65 years, is a significant health burden for the aged population [4]. Glucose-stimulated insulin production is a function of pancreatic beta-cells and is a key factor in the development of type 2 diabetes [5].

The International Diabetes Federation estimates that 463 million persons worldwide have diabetes as of its most recent data from 2019[6]. The prevalence of diabetes is rapidly increasing; according to earlier estimates from 2017, there were 425 million diabetics [7]. The number is predicted to nearly double by 2030[6].

In terms of the number of people with diabetes, Egypt is among the top 10 countries in the world [8]. If diabetes were a serious public health issue that placed a heavy weight on the Egyptian economy. The prevalence of diabetes among adults aged 20 to 79 is approximately 15.5% [9]. It is important to note that the prevalence of diabetes has sharply grown in Egypt during a relatively short period of time. The number of diabetic patients rises from 4.4 million in 2007 to 7.5 million in 2013 [8]. The unhealthy eating, sedentary lifestyle, and poor lifestyle choices of Egyptian youth may be to responsible for this worrying growth [9].

Both type 1 and type 2 diabetes mellitus are prone to the development of chronic vascular problems. Microvascular problems and macrovascular complications are the two main categories. Retinopathy, nephropathy, and neuropathy are the three most common microvascular consequences [10]. While the most prevalent macro vascular consequences of diabetes include cardiac, peripheral arterial, and cerebrovascular disorders [11].

Diabetes mellitus is the primary cause of diabetic nephropathy (DN), a chronic microvascular disease characterised by reduced renal function and increased albumin excretion in the urine. Due to end-stage renal disease, the increasing frequency of DN has also increased the morbidity and mortality of type-1 and type-2 diabetics [12]. Diabetes as chronic disease has serious complications which can affect multiple vital organ systems[13].

The severe side effect of diabetes mellitus known as diabetic nephropathy (DN) is a common pathogeny of end-stage kidney disease that has a large financial impact on human civilization worldwide. Traditional approaches including renin-angiotensin-aldosterone system blocking, blood glucose control, and bodyweight reduction may not be effective enough in many therapy practises for DN management [14].

Diabetic nephropathy is characterised by an increase in urine albumin excretion (UAE) in the absence of other renal diseases. Urinary albumin/creatinine ratio [ACR] >3.0 mg/mmol is the first clinical symptom of nephropathy, which is the presence of low but abnormal amounts of albumin in the urine (>30 mg/day or 20 g/min). Incipient nephropathy, commonly known as microalbuminuria, is a disorder where the kidneys produce insufficient levels of albumin [15].

Diabetic nephropathy (DN) is the most common cause of end-stage renal disease (ESRD) in the world. The main risk factors for the development of DN are chronic hyperglycemia and excessive blood pressure. In general, type 1 diabetes patients should be screened for microalbuminuria every year starting 5 years after diagnosis, and type 2 diabetes patients should be screened at diagnosis and every year after that. Blood glucose and blood pressure control via renin-angiotensin system blockade is standard therapy, with A1c targets of 7% and 130/80 mmHg. Albuminuria regression is still an essential therapeutic target. However, diagnosing and treating nonproteinuric DN (NP-DN), which does not follow the traditional DN pattern, can be difficult. In reality, the prevalence of DN is rising, necessitating more treatment to prevent or alleviate the condition [16].

Taurine is a sulfuric amino acid with the chemical formula NH2CH2CH2SO3H that is common in mammalian tissues. This semi-essential amino acid is obtained in the body from food consumption as well as the reaction of methionine with cysteine in the liver [17]. Evidence suggests that taurine may be a conditionally necessary amino acid in disorders like diabetes, obesity, metabolic syndrome, and atherosclerosis, which are all linked to increased oxidative stress and inflammation [17].

When compared to the control group, taurine administration reduced oxidative stress in the brain, enhanced hormone secretion, and prevented diabetic neuropathy, retinopathy, and nephropathy. Taurine has been shown to be useful in the treatment of diabetic hepatotoxicity, vascular issues, and heart injury. Taurine has been found to be useful in the treatment of oxidative stress [18].

Taurine protects against renal cell death (necrosis and apoptosis) and oxidative stress in a variety of pathophysiological conditions induced by toxins, drugs, and nephrotoxicity by increasing antioxidant enzyme activities, regulating K+–Na+–ATPase activity, and decreasing TNF- and NO synthesis in the kidney[19,20,21].

2. Material and methods

2.1. Patients

The study include eighty diabetic patients (male and female) were chosen from Ahmed Maher hospital after their approval. Beside Ten healthy volunteers enrolled as frank control group. The study protocol was

approved by the general organization for teaching hospitals and institutes. All subjects gave written informed consent after the nature of the procedure was explained.

The patients will be divided into four groups Beside frank control group.

- Group (1): frank control group (n = 10)
- Group (2): Diabetic control group (n=20).
- Group (3): Early stage of (DN) (microalbuminuria) group (n=20).
- Group (4): Before dialysis (Kidney impairment) group (n=20).
- Group (5) : After dialysis group (n=20)

2.2. Sample collections and tests

A portion of the blood was collected on EDTA for the determination of glaciated hemoglobin. The other portion left to clot for 2 hours, at 4°C without shaking, then centrifuged at 3000 r.p.m. for 20 min. The blood which collected was separated and divided into two parts. the 1st part was used to measure blood glucose., blood urea, serum creatinine, AST, ALT, cholesterol, HDL, LDLc. the 2nd part was stored in a deep freezer at -20°C till used for the assay of taurine. Serum taurine was measured using High Performance Liquid Chromatography (HPLC) according to pre-column extraction and derivatization methodology.

2.3. Statistical analysis

Data are expressed as mean ± SD. SPSS software was utilized to perform data analysis. P- value less than 0.05 was considered statistically significant diference.

3. Results

All patients (male and female) presented with diabetic nephropathy. Complete clinical examination, investigation and biochemical analysis (liver and kidney functions, lipid profile and Hb%) add to measuring FBG, HbA1c, EAG and the recent biomarker taurine, was measured for all patients and volunteers.

Table 1 Liver functions and lipid profile in different group of patients. Data are expressed as mean+- SD**,** P-value > 0.05 (ns)**,** <0.01 (significant *)**,** <0.001 (highly significant**)**,** <0.000 (extremely significant***)

	AST	**ALT**	**LDL**	**HDL**	**Cholesterol**
Normal range	<40 U/L	<50 U/L	Optimal<100. Near optimal 100-130. Board line 130-160 mg/dl	40-60 Dangerous>60 mg/dl	Board line 150-200 Risky >250 mg/dl
Frank control group (N=10)	19.3 ± 5.11	13.0 ±5.01	129.1 ± 16.5	48±11.2	166.9 ± 20.1
Controlled Diabetic Group (N=20)	22 ± 2.3	21.6 ±4.35	146.5 ± 82.5	43.5±9.8	171.6 ± 25.24
Early stage of DN group (N=20)	26.9 ±4.0	26.7 ±4.75	147.9±41.9	43.7±6	155.45±44.23

Before dialysis group (N=20)	29.7 ±6.3	26.9 ±9.07	141.2±55.8	49.2±12.2	184.9 ± 45.9
After dialysis group (N=20)	28.6 ±3.66	28.8 ±4.43	132.4±37.6	47.3±8.5	154.35 ± 41.71
P – value	0.04*	0.02*	0.63 ns	0.2 ns	0.08 ns

Table 1, recorded that Liver function in all groups demonstrated non significance between groups,but values recorded significant changes in all groups of patients related to frank control group ($p<0.05$) .in spite, lipid profile showed non significance changes ($P>0.05$) in all groups of patients compared to frank control group, but LDL-cholesterol, HDL-cholesterol and serum cholesterol showed significant change ($P<0.01$) between groups.

Table 2,show that urea and creatinine values recorded highly significant changes in all groups of patients related to frank control group ($p<0.01$), except controlled diabetic group and Early stage of diabetic nephropathy, while Albumine in serum values recorded non significant in all groups of patients related to frank control group ($P> 0.05$), in spite Albumine in urine and Alb/creat Ratio in urine values recorded extremely significant changes in all groups of patients related to frank control group ($p<0.000$). but Creat in urine recorded non significant changes in all groups of patients related to frank control group ($p> 0.05$) as shown in Table2.

Table 2 The kidney functions in different groups of patrients. Data are expressed as mean+- SD**,** P-value > 0.05 (ns) **,** <0.01 (significant *)**,** <0.001 (highly significant**)**,** <0.000 (extremely significant***)

	Creatinine	**Urea**	**Albumine in serum**	**Albumine in urine**	**Creat in urine**	**Alb/creat Ratio in urine**
Normal range	0.5-1.5 mg/dl	<50 mg/dl	3.5-5.5 mg/dl	<20 mg/L	30-220 mg/dl	<30 Microalbuminuria30-300. Clinical Albuminuria >300
Frank control group (N=10)	0.7±0.1	22.9±2.7	3.5±0.12	4.71±3.76	57.6±17.2	9.38±7.0
Controlled Diabetic Group (N=20)	0.89±0.1	32.2±3.39	3.4±0.28	7.57±5.45	63.7±32.5	11.7±5.8
Early stage of DN group (N=20)	1.48±0.28	42.9±4.3	3.8±0.23	48.4±16.5	70.7±63.2	91.3±54.1
Before dialysis group (N=20)	5.96±1.6	158.4±75	4.1±0.26	1321.8±1310.2	57.4±40.2	2386.8±1360.6
After dialysis group (N=20)	2.65±1.15	74.38±21.2	4.2±0.37	1608.2±1547.3	62.3±43.1	2638.1±1434.6
P – value	0.000***	0.000***	0.13 ns	0.000***	0.894 ns	0.000***

Table 3**,** recorded that values of Blood glucose were not the only parameter to diagnose complications of diabetes as Blood glucose of all our patients ranged between (115.2±29.7) and (241.9±46.8) as its value not parallel to the severity of disease and data recorded significant change compared to frank control group in controlled diabetic group and After dialysis group ($P<0.05$), but showed very high significance compared to frank control group in Early stage of DN group ($P<0.000$), compared to frank control group. HbA1c recorded very high significance changes in all groups of patients related to healthy control group ($P<0.001$).

The most interesting point in our result was illustrated in Table 3. When the serum level of taurine observed in the diabetic control was highly significantly less (53.8±3.66) compared to its level recorded in frank group (76.7±3.9). These levels were decreased parallel to the severity of diabetic nephropathy from Early stage of DN (42.8±2.25) to Before dialysis (33.7±2.35) and return to increase its value in After dialysis group (47.0±1.58 mmole/L)**.**

Table 3 Hb% **,** Blood glucose **,** EAG **,** HBA1c and taurine in different groups of patients. Data are expressed as mean+-SD**,** P-value > 0.05 (ns)< **,**0.01 (significant *)**,** <0.001 (highly significant**)**,** <0.000 (extremely significant***)

	Hb% (g/dl)	**Blood glucose**	**EAG**	**HBA1c**	**Taurine**
Normal range	13-16	70-140		4.5-6.5%	55-80 mmol/l
Frank control group (N=10)	12.51 ± 1.11	87.2±7.16 A	85.6±6.22	4.8±0.21	76.7±3.9
Controlled Diabetic Group (N=20)	11.63 ± 1.18	159.9±22.9	167.38±32.7	6.7±0.77	53.8±3.66
Early stage of DN group (N=20)	11.23 ± 1.18	241.9±46.8	255±80.7	10.2±2.7	42.8±2.25
Before dialysis group (N=20)	10.31 ± 2.35	146.2±40.0	152.2±49.3	6.88±1.71	33.7±2.35
After dialysis group (N=20)	11.5 ± 1.18	115.2±29.7	151.9±48.7	6.9±1.69	47.0±1.58
P – value	0.03*	0.001**	0.000***	0.001**	0.000***

4. Discussion

Now diabetes mellitus is recognized as being a syndrome, a collection of disorders that have hyperglycemia and glucose intolerance as their hallmark, due either to insulin deficiency or to impaired effectiveness of insulin's action, or to a combination of these [22]. Several studies suggest that, together with glucose variability, the variability of other risk factors, as blood pressure, plasma lipids, heart rate, body weight, and serum uric acid, might play a role in the development of diabetes complications [23]. The patients with transient exposure to hyperglycemia develop diabetic complications, including Diabetic kidney disease. Diabetic kidney disease (DKD) is the major cause of end-stage kidney disease [24].

Diabetic nephropathy (DN) is a chronic microvascular disease caused by diabetes mellitus, characterised by increased albumin excretion in the urine and decreased renal function. The rising frequency of DN has also increased the morbidity and mortality of type-1 and type-2 diabetics due to end-stage renal disease [25]. Diabetic nephropathy (DN) is a devastating consequence of diabetes mellitus and a prevalent pathogeny of end-stage kidney disease that causes considerable health problems and a significant financial burden on human civilization around the world. In many therapeutic practises for DN management, traditional techniques like as renin-angiotensin-aldosterone system blocking, blood glucose level control, and bodyweight reduction may not provide sufficient results [26].

Several studies have discovered an inverse relationship between plasma taurine levels and fasting plasma sugar (FBS), as well as diabetes complications such as diabetic nephropathy ***[27].*** When compared to the control group, taurine administration reduced oxidative stress in the brain, enhanced hormone secretion, and prevented diabetic neuropathy, retinopathy, and nephropathy. Taurine has been shown to be useful in the treatment of diabetic hepatotoxicity, vascular issues, and heart injury. Taurine has been found to be useful in the treatment of oxidative stress **[28]**. It was proved that hypoglycemic properties of taurine are mediated through an interaction of taurine with the insulin receptor [29].

The goal of our study is to investigate the correlation between serum taurine and stages of diabetic nephropathy. After full clinical examination, biochemical analysis and investigation for all patients. We selected 90 diabetic patients from Ahmed Maher Hospital after their agreement beside ten healthy volunteers.

As the mean values of ALT and AST had no significant correlation with age, family history of diabetes, mode of therapy or type of diabetes [30]. But data showed significant changes in kidney functions in all diabetic nephropathy stages compared to frank control group ($p<0.05$). That showed impaired in renal function as increment of blood urea in most groups of patients. It was reported a high frequency of dyslipidemia in patients with diabetic nephropathy than in those without diabetic nephropathy [31].

On the other hand HbA1c showed very high significant change in all patients compared to frank control group ($p<0.001$). A further concern about moving from glucose to HbA1c diagnose diabetes is that we will observe a change in prevalence of diabetes, as an elevated HbA1c does not identify exactly the same individuals as does an elevated blood glucose. Glucose levels are also susceptible to modification by short-term lifestyle intervention while HbA1c reflects glycemia over a period of 3 to 4 months. The major disadvantage of HbA1c is that there are a number of non-glycemic conditions

that interfere with the assay. In particular, alterations of red blood cell turnover (e.g. kidney failure, hematinic deficiencies, hemolysis, acute blood loss, pregnancy, and erythropoietin therapy) may affect the relationship between HbA1c and recent glycemia [32].

Our result showed that, highly significant elevation of HbA1c in all diabetic patients groups examine in this work including control diabetic group because, is related mainly to bad habit, non-regular clinically observation and bio-chemical analysis for blood glucose and other analysis including lipid profile in addition to other factor the patients visit the NIDE in late stage [9].

Serum levels of chemerin, a multifunctional peptide involved in lipid and glucose metabolism [33]. has also been found to be elevated in patients with NPDR and PDR [34].

In Ahmed Maher hospital where our patients were collected, the diagnosis mainly depend on the biochemical analysis (FBG, HbA1c, post prandial glucose).

The ordinary follow up for all chronic diabetic patient shorten in (fasting blood glucose, postprandial blood glucose, glaciated hemoglobin and glucose in urine).Those are non-sensitive to the severity of different complication of diabetes. So, we must do a regular check up by measuring serum taurine level. Measuring of taurine is predictive for any diabetic patient has taurine level less than fifty which become highly susceptible for diabetic complications.

The most impressive observation in our work is the result of taurine which showed significant decrease in its serum level in diabetic control patients(53.8 ± 3.66) when compared to frank group (76.7 ± 3.9). Which can be considered as an early sign of renal impairment and the immediate induction of its treatment. On the other stages of diabetic nephropathy, taurine level decrease parallel to the severity of diabetic nephropathy 42.8 ± 2.25, 33.7 ± 2.35respectively which are very highly significant between each other. In the after dialysis group serum taurine level rise to 47.0 ± 1.58 which is very high significance with all groups of patients.

We suggest a new classification for stages of diabetic nephropathy according to serum taurine level. The taurine level may represent another real evaluation of the possibility of patient's deterioration as shown in this study. It has been shown that the taurine level can detect any change from normal case which may anticipate any future renal impairment. But the most serious observation In the before dialysis group, Is the taurine level was exhibited value, 33.7 ± 2.35 which may considered as a pre cancer level in different organs [35,36].

So, we advise the diabetic patient to treat with special dose of taurine to guard against diabetic nephropathy. Supporting our suggestion it was postulated that taurine supplementation is beneficial to diabetic complication, including retinopathy, nephropathy, neuropathy and cardiomyopathy [37]. Taurine was also found to be beneficial in retarding the progression of diabetic nephropathy in streptozotocininduced diabetic rats when it was administrated 4 months after induction of diabetes [38].

Taurine depletion has been implicated in the development of nerve conduction slowing which could be linked to nerve metabolic, vascular, and functional deficits in diabetic neuropathy [39]. Moreover, different studies support that taurine has an efficient role in reducing plasma and liver cholesterol in hypercholesterolemia animal induced by high cholesterol diet [40]. The valuable role of taurine in preventing cardiovascular diseases was documented in a four weeks taurine supplementation study on healthy middle aged women, where taurine was found to significantly decrease the plasma levels of independent cardiovascular risk predictor, homocysteine [41].

Diabetic Nephropathy (DN) is a complication that occurs in 20–40% of all diabetic patients. Our study suggested that the diabetic nephropathy could be classified and diagnosed by serum taurine level which is simple to use, easy to remember and based on scientific evidence. We suggest new classification diabetic nephropathy patient. When taurine level measured above 55 mmole/L, it is safety margin and considered as a normal level. When the taurine level exhibited a value between 40-55 mmole/L it is risky. Moreover, taurine level less than forty (40-30 mmole/L) the diabetic patient highly susceptible for any micro vascular complication. Less than 30 mmole/L it is very high risk.

Further studies to assess the value of taurine administration on the serum level of taurine in reflection of that as protective factor in prevention of diabetic nephropathy.

Abbreviations

- DN: Diabetic Nephropathy;

- HbA1c: Glaciated haemoglobin;
- EAG: Estimated Average Glucose;
- AST: Aspertat transmenase;
- ALT: Alanin transmenase;
- HDL: High density lipoprotine;
- LDL: Low density lipoprotine;
- DM: Diabetes mellitus;
- DN: Diabetic nephropathy;
- CKD:chronic kidney disease.

5. Conclusion

Serum taurine is reduced in diabetic patients with advanced conditions of diabetic nephropathy. Taurine Level is considered as an early marker (prognostic) to detect and prevent the diabetic nephropathy complications.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Statement of ethical approval

Statement of ethical approval was obtained from Institutional ethical committee, it's certificate number-HAM00147 dated on 10/11/20021.

Statement of informed consent

This manuscript is being submitted after consent was obtained from all authors, and all authors are aware of this manuscript submission.

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