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The Possibility of using Serum Taurine Level as an Early Marker to Control Complications of Diabetic Foot

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Abstract

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

Methods: 90 diabetic patients were selected from the national institute of diabetes and endocrinology (NIDE), 80 patients suffered from diabetic foot and classified into 4 groups according to its surgical complication in their foot and 10 diabetic controlled patients not suffered from diabetic foot considered as diabetic control group. 10 frank healthy non diabetic persons enrolled as volunteers. Complete clinical examination, investigation and biochemical analysis (liver and kidney functions, lipid profile and complete blood count), add to measuring FBG, HbA1c, VEGF and the recent biomarker taurine, was measured for all patient and volunteers.

Results: The data showed non-significant change in liver functions, Kidney functions, lipid profile, CBC and serum VEGF in all patients regarding to control group ($P>0.05$). Contrary there is a significance changes in FBG and HbA1c ($P<0.05$). On the other hand, the data showed very highly significant decrease in serum taurine in all diabetic patients according to the severity of diabetic foot compared to that recorded in healthy control ($P<0.001$).

Conclusion: Serum taurine is reduced in diabetic patients with advanced surgical conditions of diabetic foot. Taurine Level is considered as an early marker (prognostic) to control complications of diabetic foot.

Keywords: Diabetes; Diabetic foot; Taurine; HbA1c; VEGF; FBG

Introduction

Diabetes mellitus (DM) appears to be a global epidemic and increasingly a major non-communicable disease threatening both affluent and non-affluent society [1,2]. More than 170 million people worldwide have diabetes, and this figure is projected to more than double by the year 2030, if the current trend is allowed to continue further [3]. The potential severity of increasing prevalence rate of diabetes in the African continent may be translated into severe economic burden, high morbidity and mortality rates that will surpass the ravages [4].

In Egypt, Diabetes is significantly increased exceeding international rates. Egypt is now ranked eighth highest in the world in terms of the disease [5]. Furthermore, reports indicate that 43% of patients with diabetes and most patients with pre-diabetes in Egypt are likely undiagnosed. Diabetes is the major cause of end-stage renal disease and leg amputation in Egypt [6].

Diabetes mellitus has been described as a heterogeneous group of disorders characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Although different classes of diabetes have been proposed, type 1 and type 2 are the commonest forms of diabetes, and could be caused by a combination of genetic and environmental risk factors [7]. The development of chronic vascular complications is common in individuals with both type 1 (T1DM) and type 2 diabetes (T2DM). These are in general, divided into micro and macro vascular complications, with the most prevalent micro vascular complications being kidney disease, blindness, and amputations. Given the morbidity and mortality associated with these complications, there is a significant treatment gap, with current therapies only slowing disease progression [8].

Many of the complications associated with diabetes are inextricably linked through abnormalities in micro vascular and macro vascular function underpinned by the metabolic anomalies resulting from chronic hyperglycemia.

As a consequence of the multisystem nature of diabetes, the development of foot lesions and subsequent healing will be influenced by the extent and severity of other complications including peripheral vascular disease, cardiovascular disease, cerebrovascular disease, retinopathy, renal failure, depression and a significantly reduced quality of life [9]. It was found that although diabetes and cancer increased with age, diabetes appeared to increase the risk of cancer, independent of age [10].

Foot ulceration is a common complication of diabetes and at any one time 2-4% of the diabetes population is likely to have an active foot ulcer and more than half of these will become infected [11]. Eighty-five percent of infected diabetic foot ulcers progress to lower limb amputation after which 5-year, mortality rates are significantly increased [9]. As diabetic foot problems quickly reach the point of no

return, it is vital to diagnose them early and provide rapid and intensive treatment. Furthermore, it is important to achieve early recognition of the at-risk foot so as to institute prompt preventive measures [12].

Taurine (2-aminoethanesulfonic acid) is widely distributed and is found in millimolar concentration in mammalian tissues. The source of taurine in body is biosynthesis and dietary intake. Taurine is synthesized from methionine and cysteine mainly in the liver. It is well-known that biosynthetic capacity of taurine is very low in human and is absent in cats, while rodents have high synthetic capacity [13].

Many evidences support that taurine is a cytoprotective agent in a variety of tissues. Taurine modulates a variety of cellular functions, including antioxidation , modulation of ion movement, osmoregulation, modulation of neurotransmitters and conjugation of bile acids [14], modulate synthesis of pro inflammatory cytokines and play an important role in initiation and progression of immune response [15], More ever it is protective against hyperglycemia [16], hypertension [17], and endothelial dysfunction [18]. It protect the integrity of the hepatic tissue by stabilizing the reactive oxygen specious mediated lipid peroxidation and protein carbonyl formation and it act as antioxidant in tamoxifen induced hepatotoxicity [19]. Taurine depletion causes various pathological conditions, including retinal degeneration, impaired in renal function, reproductive failure and dilated cardiomyopathy [20]. It was proved that three main processes that have been implicated in tumor growth; increase cell proliferation, inhibition of tumor cell apoptosis and enhanced angiogenesis [21]. Since taurine has been demonstrated to have such excellent bioactivity properties (Figures 1-5).

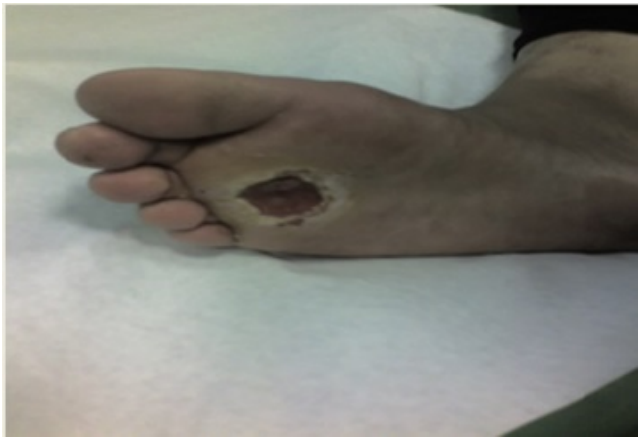

Figure 1: Right non ischemic diabetic foot with sole clean atrophic ulcer.

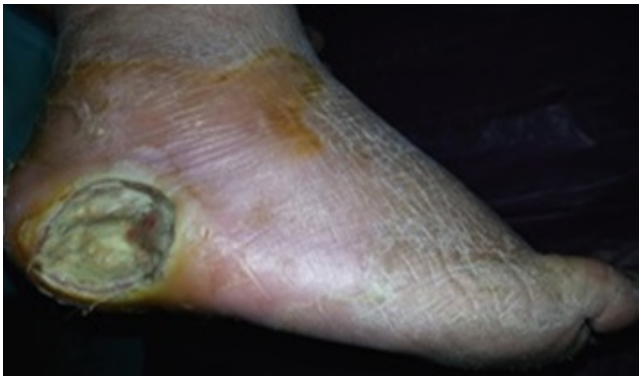

Figure 2: Right non ischemic diabetic foot with heel infected ulcer.

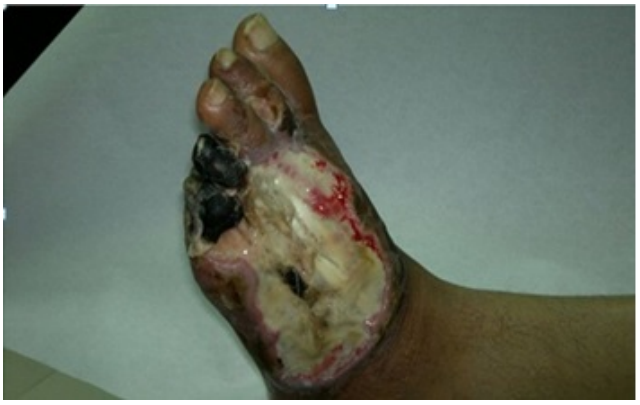

Figure 3: Left non ischemic diabetic foot with 4th, 5th toes infective gangrene with dorsum infected ulcer.

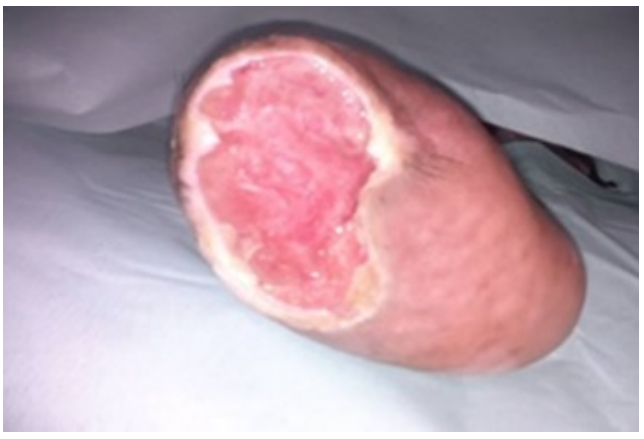

Figure 4: Right non ischemic diabetic foot with post trans-metatarsal amputation clean granulating stump.

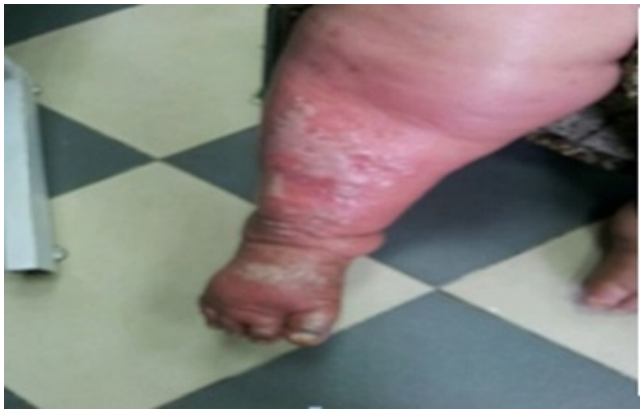

Figure 5: Right lower limb severe cellulites.

Moreover, treatment of taurine benefits many kinds of pathologies. Taurine supplementation affect against insulin dependent, non-insulin dependent diabetes mellitus and insulin resistance [13-16]. In addition, taurine supplementation is beneficial to diabetic complications, including retinopathy, nephropathy, neuropathy, atherosclerosis and cardiomyopathy [22,23]. It was suggested to use taurine as a protective substance in early pregnancy for high risk pregnant women to minimize the complication of hypertension during pregnancy [24].

In both forms of diabetes T1DM and T2DM, taurine exerts a multitude of beneficial actions. Platelet aggregation in T1DM results in an increased risk of cardiovascular incidents. When taurine is supplemented, an increase in both plasma and platelet taurine levels occur that raise the threshold at which aggregation can be triggered [25]. Taurine changes the abnormal blood lipid profile that is associated with the diabetic condition. It was proved that elevated plasma triglycerides and LDL cholesterol in diabetics were lowered through administration of taurine [26].

Vascular endothelial growth factor (VEGF) can stimulate angiogenesis, enhance collateral vessel formation, and increase the permeability of the microvasculature [27,28]. VEGF, as an important angiogenic factor plays a potent role in the formation of new vessels (angiogenesis) in the wound healing process [29,30]. Evidence exists that expression of growth factors such as VEGF reduce the occurrence of diabetic foot ulcers [31,32]. There is evidence that the expression of VEGF is reduced in patients with diabetes, and this diminution is associated with delayed healing in the wounds [31].

Materials and Methods

Patients

Our study included 80 diabetic patients selected from the outpatient surgery clinic of National Institute of Diabetes and Endocrinology (NIDE), Cairo, Egypt.

All of them suffered from diabetic foot. The study protocol was approved by Local Ethics Committee and authorized by Local Health Department. All subjects gave written informed consent after the nature of the procedure was explained.

The patients were subdivided into 4 groups:

Group (N1): Twenty patients with ulcerated diabetic foot.

Group (N2): Twenty patients with infected ulcer diabetic foot.

Group (N3): Patients with necrotic diabetic foot (gangrenous) and will need a major amputation which subdivided into two groups: 3.a. twenty patients before amputation which is named as pre-amputated group (includes finger (s) and dorsum of foot) and 3.b.twenty patients after amputation which is named post-amputated group.

Group (N): Ten controlled diabetic patients enrolled as control group (not suffered from diabetic foot and any other diabetic complications).

Group (C): Ten healthy volunteers (non-diabetic) considered as a frank control group.

Sample collections and tests

Blood samples were drawn in the morning after a 12 h fast (from 8 pm to 8 am); a portion of the blood was collected on EDTA for the determination of glaciated hemoglobin and CBC. The other portion left to clot for 2 hours, at4°C without shaking, then centrifuged at 3000 r.p.m. for 20 min.

The serum was separated was divided into two parts. The 1st part was used to measure F.B.S., blood urea, serum creatinine, AST, ALT, T.bilirubin, cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol. The 2nd part was stored in a deep freezer at -20C till used for the assay of taurine and VEGF.

Serum taurine was measured using High Performance Liquid Chromatography (HPLC) according to pre-column extraction and derivatization methodology. VEGF was measured immune-histochemistry by ELIZA.

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 difference.

Results

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

In relation to the frank control group the hematological changes in most groups of patients showed a non-significant changes (P>0.05) in Hb, RBCs, but showed a significant changes (P<0.01) in WBCs in infected ulcer group and pre-amputated gangrenous group.

PLT showed non-significant changes in all groups related to frank control group except pre-amputated gangrenous group (P<0.01) showed high significance related to frank control as demonstrated in Table 1.

	Hb (g/dl)	RBCs	WBCs	PLT
Normal range	4.5-6.5	Male: 4.7 to 6.1, Female: 4.2 to 5.4 million cells/mcL	4,500 to 10,000 cells/mcL	150.000 to 450,000/dL
Healthy control group C=10	11.63 ± 1.18	3.86 ± 0.61	6.05 ± 1.37	279.7 ± 53.79
Controlled Diabetic Group N=10	11.84 ± 1.21 A(ns)	4.18 ± 0.63 A(ns)	8.91 ± 3.93 A(ns)	296.1 ± 69.87 A(ns)
Ulcerated group N1 =20	11.65 ± 1.41 A(ns),B(ns).	4.09 ± 0.64 A(ns),B(ns)	9.46 ± 5.32 A(ns),B(ns)	256.5 ± 91.06 A(ns),B(ns)
Infected ulcer group N2 = 20	12.46 ± 1.13 A(ns),B(ns), C(ns).	4.63 ± 0.52 A(ns), B(ns), C**	10.49 ± 6.67 A*, B(ns), C(ns).	284.2 ± 63.99 A(ns),B(ns), C(ns).
Gangrenous group N3 = 20 3.a.(Pre-amputated group)	10.31 ± 2.35 A*,B*, C**, D***	3.78 ± 0.82 A(ns),B(ns), C(ns), D***	12.44 ± 8.58 A**,B(ns), C(ns), D(ns).	381.0 ± 143.75 A**,B*,C***, D**
Gangrenous group N3 =20 3.b.(Post-amputated group)	12.51 ± 1.11 A(ns),B(ns), C(ns), D(ns), E***	4.24 ± 0.56 A(ns),B(ns), C(ns), D(ns), E*	7.59 ± 2.01 A(ns),B(ns), C(ns), D(ns), E**	264.35 ± 82.35 A(ns),B(ns), C(ns), D(ns), E***

The mean difference is significant at the 0.05 level. Data are expressed as mean ± SD

A: refers to healthy control group B: refers to diabetic control group C: refers to ulcerated group D: refers to infected ulcer group E: refers to gangrenous group (pre-amputation)

p value>0.05 Non-significant(ns), p value 0.01 to 0.05 Significant *, p value 0.001 to 0.01 High significant **, p value 0.0001 to 0.001 Extremely significant***.

Table 1: Blood picture in different groups of patients.

Table 2, recorded that 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.

	Cholesterol	Triglycerides	HDL	LDL	VLDL
Normal range	Dangerous <200, board line 150-200 Risky>250 mg/dl	Desirable <150, board line 150-200 High>200mg/dl	40-60 Dangerous>60 mg/dl	Optimal <100, near optimal 100-130, board line130160mg/dl	5 - 40 mg/dL
Healthy control group C=10	166.9 ± 20.1	135.2 ± 37.9	32.1 ± 5.93	107.8 ± 27.55	26.9 ± 7.58
Controlled Diabetic Group N=10	171.6 ± 25.24 A(ns)	166.2 ± 68.5 A(ns)	30.3± 4.7 A(ns)	108.0 ± 31.1 A(ns)	33.2 ± 13.6 A(ns)
Ulcerated group N1 =20	195.2 ± 36.6 A(ns), B(ns).	176.8 ± 72.8 A(ns), B(ns).	38.4± 13.1 A(ns), B*	120.1 ±32.7 A(ns), B(ns).	38.1 ± 15.4 A(ns), B(ns).
Infected ulcer group N2 = 20	184.9 ± 45.9 A(ns), B(ns), C(ns).	180.7±120.5 A(ns), B(ns), C(ns).	28.7± 8.7 A(ns), B(ns), C***	138.3 ± 29.3 A*, B*, C(ns).	36.1 ± 24.1 A(ns), B(ns), C(ns).
Gangrenous group N3 =20 3.a.(Pre-amputated group)	155.45±44.23 A(ns), B(ns), C**, D*	156.2 ± 58.69 A(ns), B(ns), C(ns), D(ns)	30.2 ± 6.48 A(ns), B(ns), C**, D(ns)	93.75 ± 38.12 A(ns), B(ns), C*, D***	31.27 ± 11.76 A(ns), B(ns), C(ns), D(ns).
Gangrenous group	154.35 ± 41.71	151.9 ± 40.42	32.45 ± 5.91	91.45 ± 39.66	30.38 ± 8.09

N3 =20 3.b.(Post-amputated group)	A(ns), B(ns), C**, D* , E(ns	A(ns), B(ns), C(ns), D(ns), E(ns)	A(ns), B(ns), C*, D(ns), E(ns).	A(ns), B(ns), C*, D***, E(ns).	A(ns), B(ns), C(ns), D(ns), E(ns)
The mean difference is significant at the 0.05 level. Data are expressed as mean ± SD.*A: refers to healthy control group B: refers to diabetic control group: refers to ulcerated group D: refers to infected ulcer group E: refers to gangrenous group (pre-amputation) p value>0.05 Non-significant(ns),p value 0.01 to 0.05 Significant *,p value 0.001 to 0.01 High significant **,p value 0.0001 to 0.001 Extremely significant***.					

Table 2: Lipid profile in different groups of patients.

Liver function in all groups demonstrated non significance between groups, except liver enzymes (AST,ALT) in ulcerated group which showed high significant change (P<0.01) compared to frank control group. Also urea and creatinine values recorded significant changes in all groups of patients related to frank control group (p<0.05), except controlled diabetic group and ulcerated group for urea, while creatinine value recorded significance in ulcerated group and infected ulcer group and gangrenous group (post-amputated group) (P<0.01), and very high significance in gangrenous group (pre-amputated group) (P<0.000) related to frank control group as shown in Table 3.

	AST	**ALT**	**T.Billi**	**Urea**	**Creat**
Normal rang	>40 U/L	>60 U/L	0.2-1.2 mg/dL	<50 mg/dl	0.5-1.5 mg/dl
Healthy control group **C=10**	19.6 ± 6.63	16.2 ± 6.49	0.52 ± 0.26	30.1 ± 8.07	0.59 ± 0.34
Controlled Diabetic Group **N=10**	25.8 ± 11.51 A(ns)	26.3 ± 18.83 A(ns)	0.57 ± 0.29 A(ns)	41.0 ± 12.7 A(ns)	1.18 ± 0.26 A(ns)
Ulcerated group **N1=20**	46.9 ± 31.8 A**, B(ns)	43.3 ± 28.47 A**, B(ns)	0.49 ± 0.36 A (ns), B (ns).	60.3 ± 49.4 A(ns), B(ns)	1.2 ± 0.93 A*, B(ns)
Infected ulcer group **N2=20**	23.8 ± 8.46 A(ns), B(ns), C**	17.7 ± 6.97 A(ns), B(ns), C**	0.40 ± 0.17 A(ns), B(ns), C (ns).	64.7 ± 43.3 A*, B(ns), C(ns)	1.28 ± 0.62 A*, B(ns), C(ns).
Gangrenous group **N3=20** **3.a.(Pre-amputated group)**	34.3 ± 25.85 A(ns), B(ns), C(ns), D(ns)	29.7 ± 27.75 A(ns), B(ns), C(ns), D(ns)	0.495 ± 0.26 A(ns), B(ns), C (ns), D(ns).	70.99 ± 49.36 A*,B (ns), C (ns), D(ns).	1.49 ± 0.73 A**, B(ns), C (ns), D(ns).
Gangrenous group **N3=20** **3.b.(Post-amputated group)**	33.8 ± 22.31 A(ns), B(ns), C(ns), D(ns) ,E(ns)	31.5 ± 26.34 A(ns), B(ns), C*, D(ns), E(ns)	0.57 ± 0.23 A(ns),B(ns), C(ns), D(ns), E(ns)	63.48±47.89 A*, B(ns), C(ns), D(ns), E(ns)	1.29± 0.65 A*, B(ns), C(ns), D(ns), E*
The mean difference is significant at the 0.05 level. Data are expressed as mean ± SD A: refers to healthy control group B: refers to diabetic control group C: refers to ulcerated group D: refers to infected ulcer group E: refers to gangrenous group (pre-amputation) p value>0.05 Non-significant(ns),p value 0.01 to 0.05 Significant *p value 0.001 to 0.01 High significant **p value 0.0001 to 0.001 Extremely significant***					

Table 3: Liver enzymes and kidney functions in different groups of patients.

In Table 4, values of FBG were not the only parameter to diagnose complications of diabetes as FBG of all our patients ranged between (179.7 ± 76.41) and (271.2 ± 130.78) 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 gangrenous group (post-amputated) (P<0.05), but showed very high significance compared to frank control group in ulcerated and infected ulcer groups (P<0.000), and high significant changes in gangrenous group (pre-amputated group) (P<0.00) compared to frank control group.

HbA1c recorded very high significance changes in all groups of patients related to healthy control group (P<0.000). VEGF values showed significant changes in diabetic control group and high significance changes in gangrenous group (pre-amputated) related to healthy control group, but other groups of patients showed non significance changes compared to healthy control group.

Photographs taken from different groups of patients showed different stages of diabetic foot. Photo (1) showed right non ischemic diabetic foot with sole clean atrophic ulcer (ulcerated group), photo (2) showed right non ischemic diabetic foot with heel infected ulcer (infected ulcer group), photo (3) showed left non ischemic diabetic foot with 4th,5th toes infective gangrene with dorsum infected ulcer (pre-amputation gangrenous group), and photo (4) showed right non

ischemic diabetic foot with post trans-metatarsal amputation clean granulating stump (post-amputation gangrenous group).

	FBG	HbA1c	VEGF	Taurine
Normal range	70-120 mgldl	4.5-6.5 g/dl	30-1200 pg/ml	55-65 mmol/l
Healthy control group C=10	97.6 ± 5.56	5.94 ± 0.32	68.91 ± 13.7	63.5 ± 4.0
Controlled Diabetic Group N=10	215.5 ± 102.3 A^{*}	8.91 ± 1.3 A^{***}	167.03 ± 19.86 A^{*}	4.16 39.12 ± A^{***}
Ulcerated group N1=20	271.2 ± 130.78 A^{***}, B(ns)	9.9 ± 1.29 A^{***}, B(ns)	82.76 ±7.68 A(ns), B^{*}	34.32 ± 1.62 A^{***},B^{***}
Infected ulcer group N2=20	246.1 ± 102.55 A^{***}, B(ns), C(ns)	9.1 ± 1.36 A^{***},B(ns) ,C(ns)	75.94 ± 9.11 A(ns), B^{*},C(ns)	28.9 ± 1.06 A^{***}, B^{***}, C^{***}
Gangrenous group N3=20 3.a. (Pre-amputated group)	223.1 ± 121.54 A^{**},B(ns), C(ns), D(ns)	9.72 ± 2.51 A^{***},B(ns), C (ns), D(ns).	202 ± 18.28 A^{**}, B(ns), C^{***}, D^{***}	21.99 ± 1.65 A^{***},B^{***}, C^{***}, D^{***}
Gangrenous group N3=20 3.b. (Post-amputated group)	179.7 ± 76.41 A^{*},B(ns), C^{**}, D^{*}, E(ns).	8.61 ± 1.56 A^{***}, B(ns), C(ns), D(ns), E^{*}.	145.32 ± 19.12 A(ns), B(ns), C(ns), D^{*}, E (ns).	29.75 ± 2.35 A^{***},B^{***}, C^{***}, D(ns), E^{***}
The mean difference is significant at the 0.05 level. Data are expressed as mean ± SD A: refers to healthy control group B: refers to diabetic control group C: refers to ulcerated group D: refers to infected ulcer group E: refers to gangrenous group (pre-amputation) p value>0.05 Non-significant(ns), p value 0.01 to 0.05 Significant *p value 0.001 to 0.01 High significant **p value 0.0001 to 0.001 Extremely significant***				

Table 4: Fasting blood glucose (FBG), Glaciated hemoglobin (HbA1c), vascular endothelial growth (VEGF) and serum taurine level in different groups of patients.

The most interesting point in our result was illustrated in Table 4. When the serum level of taurine observed in the diabetic control was highly significantly less (39.12 ± 4.16) compared to its level recorded in frank group (63.5 ± 4.0). These levels were decreased parallel to the severity of diabetic foot from ulcer (34.32 ± 1.62) to infected ulcer (28.9+ 1.06) to gangrenous foot (pre-amputation) (21.99 ± 1.65) and return to increase its value in post-amputated group (29.75 ± 2.35 mmole/L).

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 [33]. Moreover, experiencing micro vascular complications is associated with a greater risk of macro vascular complications, including coronary heart disease and cerebrovascular diseases [34]. Since prevention is more cost-effective than the treatment of diabetes complications, there is indeed a pressing need for more evidence to support efficacious preventive strategies that could delay or avert the development and progression of micro vascular complications in diabetic populations, especially diabetic foot [35]. Diabetic neuropathy, in combination with the occurrence of other complications, such as peripheral vascular disease, can result in diabetic foot disease and is the leading cause of amputation [34].

The natural history of the diabetic foot can be divided into six stages, stage one: The foot is not at risk, stage two: The patient has developed one or more of the risk factors for ulceration of the foot, stage three: This is usually an ulcer, stage four: The ulcer has developed infection with the presence of cellulites, stage five: Necrosis has supervened, stage six: The foot cannot be saved and will need a major amputation [12]. Management of diabetic foot ulcers (DFU) is a long and complex process that begins before ulcer formation through a program of prevention [9].

Different physiological functions and roles are modulated by taurine among these are: antioxidation; osmoregulation; membrane stabilization; conjugation of bile acids; neuromodulation; detoxification; and regulation of calcium homeostasis. Clinically, prophylactic and therapeutic taurine supplementation showed a beneficial effectiveness in a broad spectrum of oxidative stress-induced pathologies and clinical conditions including: hepatotoxicity and hepatic disorders; renal disorders; epilepsy and other seizure disorders; cardiomyopathy; cystic fibrosis; alcoholism; Alzheimer's disease; growth retardation; retinal degeneration; and diabetes mellitus[36-38].

It was proved that hypoglycemic properties of taurine are mediated through an interaction of taurine with the insulin receptor [39]. The

protective effects of taurine in diabetic-animal models T1DM and T2DM are shown in several investigations that included mice, rats and rabbits. The exact mechanisms by which taurine exerts its protective functions and on glucose homeostasis have been explored but not totally resolved yet [40, 41].

The goal of our study is to investigate the correlation between serum taurine and stages of diabetic foot. After full clinical examination, biochemical analysis and investigation for all patients beside surgical examination. We selected 90 diabetic patients from National Institute of Diabetes And Endocrinology (NIDE) after their agreement beside ten healthy volunteers. All the patients examined revealed no significant changes in liver functions, lipid profile and VEGF.

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 [42]. But data showed significant changes in kidney functions in all diabetic foot stages compared to frank control group ($p<0.05$). That showed mild 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 foot ulcers than in those without diabetic foot [43].

It was suggested that the increase in blood glucose tend to rise of VEGF level in blood stream in all diabetic patients [44]. Progressive decrease in blood supply in skeletal muscle stimulates ulceration, ischemic and non-ischemic infection. So, haw is VEGF involved in the pathophysiology of diabetic wound healing? Recently, it was approved that, the VEGF level reduced in patients with diabetes especially in diabetic retinopathy [45]. Other study observed that mild decrement in VEGF level was observed in diabetic infected mice [46]. Whatever, in our data result showed that the increment of VEGF was statically significant compared to frank control but still in normal range (30-1200 pg/ml) according to our lab of NIDE. Confirming our observation, it was suggested that the VEGF may also have a future role as adjunctive therapy of diabetic complications [47].

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 [33].

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 [6]. But, attracted our tension is significant decreased in its level in gangrenous group (post amputated group).

The most impressive observation in our work is the result of taurine which showed very highly significant decrease in its serum level in diabetic control patients(39.12 ± 4.16) when compared to frank group (63.5 ± 4.0). Which can be considered as an early sign of foot impairment and the immediate induction of its treatment. On the other stages of diabetic foot, taurine level decrease parallel to the severity of diabetic foot 34.32 ± 1.62, 28.9 ± 1.06, 21.99 ± 1.65 respectively which are very highly significant between each other. In the post amputated group serum taurine level rise to 29.75 ± 2.35 which is very high significance with all groups of patients except infected ulcer group (28.9 ± 1.06).

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.

We suggest a new classification for stages of diabetic foot 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 foot problem. But the most serious observation In the pre-amputated stage, Is the taurine level was exhibited value, 21.99 ± 1.65 which may considered as a pre cancer level in different organs [48,49].

So, we advise the diabetic patient to treat with special dose of taurine to guard against diabetic foot. Supporting our suggestion it was postulated that taurine supplementation is beneficial to diabetic complication, including retinopathy, nephropathy, neuropathy and cardiomyopathy [20]. Taurine was also found to be beneficial in retarding the progression of diabetic nephropathy in streptozotocin-induced diabetic rats when it was administrated 4 months after induction of diabetes [50].

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 [51]. Moreover, different studies support that taurine has an efficient role in reducing plasma and liver cholesterol in hypercholesterolemia animal induced by high cholesterol diet [52]. 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 [53].

A person with diabetes has a lifetime risk of foot ulceration of between 15 and 25%. The identification of relevant risk factors is essential for all patients with diabetes. Our study suggested that the diabetic foot 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 foot patient. When taurine level measured above fifty mmole/L, it is safety margin and considered as a normal level. When the taurine level exhibited a value between 40-50 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 foot problems.

Conclusion

Our study demonstrated that serum taurine level could be used as early marker in the detection and prevention of diabetic foot complications.

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