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TO EVALUATE THE LEVELS OF HOMOCYSTEINE AND ZINC IN PATIENT WITH VARIABLE DURATION OF TYPE 2 DIABETES MELLITUS.

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ABSTRACT
The purpose of present study was to explore the association of Homocysteine (Hcy) status and zinc levels in diabetic Patients of different duration. The levels of reactive oxygen species and oxidized products in diabetic patients are concern for the complication of the diabetes. Elevated (Hcy) blood levels are responsible for endothelium damage causing blood vessel inflammation which in turn may lead to atherogenesis and resulting ischemic injury. The toxic influence of Hcy to the endothelium can be blocked by antioxidant enzyme supplementation. To achieve this objective diabetes mellitus type 2 patients(DMT2) were divided into 3 groups and controls based on duration of sufferings from diabetes. Total 120 subjects, 30 were assigned as control, (group 1) and 90 of DMT2. Patients of DMT2 were divided into; group 2 (DMT2 <5 years), group 3 (DMT2 = 5-10 years) and group 4 (DMT2 >10 years). DMT2 was diagnosed according to guidelines of American Diabetes Association. It was found that the levels of circulating homocysteine were considerably higher in patients having type2 diabetes. Moreover, It was interestingly noted that the serum homocysteine level rises with the long duration of diabetes. A rise of Hcy in plasma has been recognized as a threat for many complications in diabetes. Alteration of total antioxidant profile along with levels of zinc in different durations of diabetes has been a major focus of current research.

KEYWORDS: Homocysteine, Reactive oxygen species, Diabetes Mellitus Type 2 (DMT2), Atherogenesis.

INTRODUCTION
Diabetes mellitus (DM) is cluster of metabolic disorders which is characterized by chronic symptom including metabolic disturbances of lipids, proteins and carbohydrates, ensuing from imperfectness in either the secretion of hormone, its action, or both.[1] This can be characterized by chronic elevated plasma glucose levels and its development and prognosis related to multiple factors as genetic or family history and pre or postnatal environmental factors[2] Glucolipotoxicity will harm differing types of cells by a variety of mechanisms as well as aerobic stress which may be a typical link.[4] The term "oxidative stress" has been used once reactive oxygen species (ROS) and reactive nitrogen species (RNS) reach excessive levels, either by excess production or insufficient removal. Being extremely reactive molecules, the consequence of ROS and RNS excess is to harm proteins, lipids and DNA.[5] Diabetes could be a documented biggest threat to the world as epidemic diseases. In 2013, according to International diabetic Federation, calculable 381 million individuals had diabetes. Its prevalenceis increasing gradually, and by 2030, this range is calculable to virtuallydouble.[6]

The aerobic stress, through ROS, has been projected because the root reason for insulin resistance, β-cell dysfunction, impaired glucose tolerance and diabetic complications like stroke,cardiovascular illness, chronic renal failure, foot ulceration and retinopathy.[7] In symptom, overload cells with energysubstrate, augment the flux of electron donors(NADH and FADH2) to mitochondrial transport chain, end in excessive production of superoxide anion radical (•O2−).[5] This ends up in metabolic events like increased polyol pathway activity, excess formation of advanced glycation products, protein kinase C and nuclear transcription factor κb activation and increased hexosamine pathway flux.[6] In glucose-mediated stress pathway it activates RUNX2 DNA-binding transcription which plays a very important role in epithelial tissue cell function and growing, cause micro- vascular complications (diabetic retinopathy, diabetic neuropathy, diabetic nephropathy) and macrovascular complications (coronary artery

illness, stroke, peripheral vascular disease) and insulin resistance due to impaired signals.[8]

Homocysteine is an endogenous S-containing amino acid intermediate of the methionine and is not obtained from the diet. Methionine enters the one-carbon cycle either through diet having methionine-containing protein or by endogenous protein breakdown. It is then converted to *S*-adenosylmethionine, which is a universal methyl donor for important acceptors, like nucleic acids, neuro-transmitters, hormones. High blood total homocysteine(tHcy) level is risky factor for both cardiovascular and noncardiovascular- mortality[9] and responsible for epithelium harm inflicting blood vessel inflammation that successively might lead to pathology and ensuing ischemic injury.

Hyperhomocysteinemia is thus a double risk issue for coronaries. The superoxide ion formed by homocysteine autooxidation can cause vascular injury by chemical reaction of lipoprotein. Besides, Hcy affects nitric oxide binding or production, that hinders vasodilatation. Hcy induces a procoagulativestate by increased thromboxane formationand platelet aggregation, coagulation factor activation factor XII, inhibition of protein C activator, and the facilitation of lipoprotein binding to fibrin. The toxic influence of Hcy to the epithelium are often blocked by antioxidant supplementation. Hcy levels can be reduced by vitamin B administration whereas the production and effects of free radicals are often controlled by antioxidants.[10,11]

Many diseases processes are interconnected with low antioxidant defense and high oxidative stresses.[12] Zinc (Zn) has a crucial role in the formation, storage and utilization of the insulin. Zinc is insulin stimulator, role in occurrence of diabetes and lowered in diabetes[15] When there is problem in β cells, the zinc levels also altered. Zinc has powerful role to decrease hyperglycemia along with its strong protective action in response to ox. stress which can lead to chronic diabetic problems. Regarding chronic stages of diabetes shows that high plasma copper levels and low zinc in diabetes as of normal and in the individuals with diabetes without any chronic problems.[13] It plays an extensive role in protein functioning, immune system and acts as ionic signaling. Various enzyme and protein transcription factors depend on zinc for their proper functioning. It also used in treatment of large number of infections (bacterial and viral). It is considered non toxic, as it is an essential trace element. Its deficiency is common which result in effects on growth, development, immunity, sexual health.[14]

Zinc is integral part of various proteins having antioxidant functions (Zn-Cu SOD). It acts by inhibiting NADPH oxidase thus lowering the formation of free radicals and also cytokines thru regulation of a Zinc finger protein A20. A20 leads to hinderence in NF-κB stimulation via TRAF pathway.[16] It acts as an anti inflammatory agent in addition to its antioxidant activity. Zinc act against oxidants so if it is given in the preliminary stage in diabetes, it will protect against ox. stress.[17]

Zinc is believed to be involved in regulating Hcy levels via mediating methionine synthase(MS) and betaine homocysteine methyl transferase(BHMT), both of which are Zn-dependent metallo-enzymes so it may be hypothesized that their levels are associated with the risk of diabetic complications. Cobalamin-dependent methionine synthase (MetH) is an important metalloenzyme responsible for the biosynthesis of methionine. It catalyzes methyl transfer from N^5-methyl-tetrahydrofolate to Hcy by using a zinc ion to activate the Hcy substrate[18] Homeostasis of Hcy will be disturbed by Zn deficiency but not by supplements, and elevated serum Hcy levels could be due to decreased expression of MS during Zn deficiency.[19]

MATERIAL AND METHODS

The study was conducted in Baqai Medical University. Protocol was approved by the Ethics Committee, Faculty of Medicine, Baqai Medical University. Subjects were selected according to inclusion criteria from patients admitted to the OPD of Diabetes Centers. Patients are adult males, aged 25 - 65, willing to be included in the study. All of them were explained about the nature of the study and had to authorize the ethical consent. Demographic and anthropometric data, and past medical history and medications, were recorded.

120 patients 90 with type 2 DM and 30 Controls were included. Controls were in group 1 and subjects with DM type 2 were divided into 3 subgroups according to the American Diabetes Association criteria for diagnoses of diabetes Group 2 with duration <5 years, group 3 with duration 6-10 years and group 4 with duration >10 years Subjects excluded from the study were with coronary artery diseases, on Antioxidant, renal failure and thyroid disease. Diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association. New patients should not be on oral hypoglycemicagents, aspirin, insulin, statin and anti-hypertensive medications. Subjects with diabetes duration five years and more must have normal LDL-cholestrol according to the adult treatment panel (ATP) III guideline. Blood samples were collected following overnight fasting about 8 hours. The fasting plasma glucose (FPG), haemoglobin A1c(HbA1c), homocysteine, zinc levels and total antioxidant capacity were analysed. Glucose levels were carried out using the glucose oxidase method. HbA1c was determined by automated kit on cobas integra provided by Roche. The AxSYM HCY assay is based on the FPIA(Fluorescence Polarization Immunoassay) technology. Bound homocysteine (oxidized form) is reduced to free homocysteine that is enzymatically converted to SAH (Sadenosyl-L-homocysteine) as, Reduction Free homocysteine is formed by the reduction of homocystine, mixed disulfide and protein-bound

forms of homocysteine in the sample by the use of DTT(dithiothreitol). Enzymatic Conversion Free homocysteine is converted to S-adenosyl-Lhomocysteine hydrolase the use of S-adenosyl-L-homocysteinehydrolase and excess adenosine.

Zinc analysis was carried by direct calorimetric kit by SPINREACT Spain. It is usually based on direct calorimeter testing specimen. It forms a color compound by reacting with specific complex5 Br- PAPS at a pH of 8.6 in a buffered media. The quantity of zinc is proportional to color intensity in the sample.

RESULTS

Table 1: Variables Between Normal Control Group and Diabetics Patients of 5 year Duration. (p<0.001) IS Considered To Be Significant.

Variables	1 (Normal Control)	2 (diabetics till 5 yrs duration)	CI 95%		P.Value
			Upper	Lower	
Age	53.56 ± 10.0	53.63 ± 9.30	-5.060	- 4.926	0.979
Weight	71.23 ± 5.96	64.73 ± 7.36	3.030	9.969	<0.001
Systolic. Pr	151.00 ± 8.38	147.6 ± 10.23	-1.435	8.235	0.165
Diastolic. Pr	87.33 ± 3.67	88.63 ± 3.81	-3.235	0.635	0.184
FBS	87.10 ± 13.88	188.0 ± 49.80	-119.795	- 82.004	<0.001
HbA1c	4.91 ± 0.989	8.41 ± 1.87	- 4.273	- 2.726	<0.001
Hcy	11.92 ± 4.63	13.29 ± 3.83	-3.561	0.816	0.215
Zn	82.0 ± 24.21	75.00 ± 24.93	- 5.702	19.702	0.275
TAC	1.00 ± 0.13	1.04 ± 0.10	- 0.0986	0.024	0.234

A significant difference was noticed when weight in Kg (p<0.001), fasting blood sugar p<0.001, HbA1c (p=0.000), among the groups. However these were not-significant when systolic pressure (p=0.615), diastolic pressure (p=0.184) and homocycteine (p=0.215), were compared. A same trend of non significance were noticed between the two groups when levels of zinc (p=0.275), and TAC (p=0.234) between the normal controls and patients with 5 year diabetes mellitus.

Table 2: Variables Between Normal Controls And Diabetics Of 5-10 Years.

Variables	1(normal control)	(diabetics 5-10 yrs duration)	CI 95%		P.Value
			Upper	lower	
Age	53.56 ± 10.0	56.26 ± 9.79	-7.816	2.416	0.295
Weight	71.23 ± 5.96	68.60 ± 7.78	- 0.955	6.22219	0.147
Systolic. Pr	151.00 ± 8.38	149.4 ± 8.16	-2.676	5.876	0.457
Diastolic. Pr	87.33 ± 3.67	88.76 ± 3.89	-3.388	0.521	0.148
FBS	87.10 ± 13.88	182.83 ± 44.75	-112.858	-78.608	<0.001
HbA1c	4.91 ± 0.989	8.08 ± 1.79	-3.922	-2.424	<0.001
Hcy	11.92 ± 4.63	17.89 ± 6.57	-8.900	-3.033	<0.001
Zn	82.0 ± 24.21	78.03 ± 26.39	-9.122	17.056	0.546
TAC	1.00 ± 0.13	0.79 ± 0.09	0.150	0.269	<0.001

(p<0.001) IS CONSIDERED TO BE SIGNIFICANT

A statistically significant difference was noticed regarding fasting blood sugar (p<0.001), HbA1c (p<0.001), and homocysteine (p=0.000) were compared. A similar significant difference was TAC (p<0.001) were compared between these two groups. When the levels of weight (p=0.147), systolic pressure (p=0.457), diastolic pressure (p=0.148), zinc (p=0.546), and copper (p=0.941) were not significant when analyzed between these groups.

Table 3: Variablesbetween Normal Controls and Diabetics of More Than 10 Years.

Variables	1(Normal Control)	4 DIABETICS >10YRS)	CI 95%		P.Value
			lower	Upper	
Weight	71.23 ± 5.96	69.29 ± 8.68	-1.887	5.820	0.311
Age	53.56 ± 10.0	54.80 ± 9.55	-6.290	3.823	0.627
Systolic. Pr	151.00 ± 8.38	151.63 ± 6.61	-4.535	3.269	0.746
Diastolic. Pr	87.33 ± 3.67	88.56 ± 3.70	-3.138	0.671	0.200
FBS	87.10 ± 13.88	160.47 ± 28.0	-84.790	-61.942	0.000
HbA1c	4.91 ± 0.989	8.77 ± 1.44	-4.498	-3.221	0.000
Hcy	11.92 ± 4.63	27.7 ± 6.74	-18.816	-12.848	0.000
Zn	82.0 ± 24.21	72.50 ± 23.52	-2.836	21.836	0.129
TAC	1.00 ± 0.13	0.47 ± 0.143	0.464	0.607	0.000

(p<0.001) IS Considered To Be Significant

A statistically significant difference was noticed regarding fasting blood sugar (p<0.001), HbA1c (p=0.000) and homocysteine (p<0.001) when normal controls were compared with diabetics of more than 10 years duration. A similar significant difference was seen with and TAC (p<0.001) were analyzed between these two groups. When the levels of weight (p=0.311), systolic pressure (p=0.746), diastolic pressure (p=0.200) and zinc (p=0.129), were not significant when analyzed between these groups.

Table 4: Comparison Between Diabetics, 5years and Diabetics Of 5-10 Years.

VARIABLES	2 DIABETICS <5YRS)	3 (DIABETICSB/W 5-10YRS)	CI 95%		P.Value
			Lower	Upper	
Weight	64.73± 7.36	68.60 ± 7.78	-7.783	0.0501	0.057
Age	53.63 ± 9.30	56.26 ± 9.79	-7.6596	2.3030	0.290
Systolic. Pr	147.6 ± 10.23	149.4 ± 8.16	-6.5854	2.985	0.455
Diastolic. Pr	88.63 ± 3.81	88.76 ± 3.89	-2.1262	1.859	0.894
FBS	188.0± 49.80	182.83± 44.75	-19.302	29.636	0.674
HbA1c	8.41 ± 1.87	8.08 ± 1.79	-0.62074	1.274	0.493
Hcy	13.29± 3.83	17.89± 6.57	-7.376	-1.812	0.002
Zn	75.00 ± 24.93	78.03 ± 26.39	-16.303	10.236	0.649
TAC	1.04± 0.10	0.79± 0.09	0.196	0.297	<0.001

(p<0.001) IS CONSIDERED TO BE SIGNIFICANT

A significant difference regarding homocysteine (p=0.002), and TAC (p<0.001) was seen between the diabetic patients of 5 years and of 5-10 years duration. The difference between weight (p=0.057), systolic pressure (p=0.455), diastolic pressure (p=0.894), fasting blood sugar (p=0.674) and HbA1c (p=0.493) were found to be statistically non-significant. A similar trend of non-significance was found when zinc (p=0.649) were compared between the groups.

Table 5: Diabetics of 5 Years and Diabetics of More Than 10 Years Duration.

Variables	2(Diabetics <5 Years)	4(Diabetics > 10YRS)	CI 95%		p Value
			Lower	Upper	
Weight	64.73 ± 7.36	69.29 ± 8.68	-8.694	-0.372	0.033
Age	53.63 ± 9.30	54.80 ± 9.55	-6.041	3.708	0.634
Systolic. Pr	147.6 ± 10.23	151.63 ± 6.61	-8.487	0.421	0.075
Diastolic. Pr	88.63 ± 3.81	88.56 ± 3.70	-1.877	2.010	0.946
FBS	188.0 ± 49.80	160.47 ± 28.0	6.652	48.414	0.011
HbA1c	8.41 ± 1.87	8.77 ± 1.44	-1.222	0.502	0.407
Hcy	13.29 ± 3.83	27.7± 6.74	-15.277	-7.961	<0.001
Zn	75.00 ± 24.93	72.50 ± 23.52	-10.027	15.027	0.691
TAC	1.04 ± 0.10	0.47 ± 0143	0.508	0.637	<0.001

(p<0.001) IS CONSIDERED TO BE SIGNIFICANT

Table 5 showed a significant difference regarding homocysteine (p=0.000), fasting blood sugar (p=0.011) and TAC (p=0.000) was seen between the diabetic patients of 5 years and those of >10 years duration. The difference regarding weight (p=0.033), systolic pressure (p=0.075), diastolic pressure (p=0.946), and HbA1c (p=0.407) were found to be statistically non-significant. A similar trend of non-significance was found when zinc (p=0.691), compared between the groups.

Table 6: Comparison of Variable Between Diabetics Of 5-10 Yrs Duration And Those Of More Than 10 Yrs Duration.

Variables	3(Diabetics B/W5-10 YRS)	4(Diabetics > 10 Years)	CI 95%		P.Value
			Lower	Upper	
Weight	68.60 ± 7.78	69.29 ± 8.68	-4.92814	1.42119	0.359
Age	56.26 ± 9.79	54.80 ± 9.55	-3.53356	6.46689	0.559
Systolic. Pr	149.4 ± 8.16	151.63 ± 6.61	-6.07363	1.60697	0.249
Diastolic. Pr	88.76 ± 3.89	88.56 ± 3.70	-1.76307	2.16307	0.839
FBS	182.83 ± 44.75	160.47 ± 28.0	3.07311	41.66023	0.024
HbA1c	8.08 ± 1.79	8.77 ± 1.44	-1.52765	.15432	0.108
Hcy	17.89 ± 6.57	27.7 ± 6.74	-11.00864	-2.85470	<0.001
Zn	78.03 ± 26.39	72.50 ± 23.52	-7.38707	18.45373	0.395
TAC	0.79 ± 0.09	0.47 ± 0143	.19680	.29720	<0.001

(p<0.001) IS CONSIDERED TO BE SIGNIFICANT

Table 6 showed significant difference regarding homocysteine (p=0.001) and TAC (p<0.001) was seen between the diabetic patients of 5-10 years and those of more than 10 years duration. The difference between weight (p=0.359), systolic pressure (p=0.249), diastolic pressure (p=0.839), fasting blood sugar (p=0.024) and HbA1c (p=0.108) were found to be statistically non-significant. A similar trend of non-significance was found when zinc (p=0.395)was compared between the groups.

DISCUSSION

Diabetic subjects are prone to vascular problems and when it is of long duration leads to athresclerosis. Risk factors for vascular diseases i.e. homocysteine (Hcy) a sulphur containing amino acid and zinc along with total antioxidant capacity were investigated in diabetes mellitus type 2(DMT2) patients of variable durations. In this study Hcy levels and the relationship between Hcy and zinc in patient population devoid of factors influencing Hcy and zinc metabolism, like coronary artery diseases, smoking, renal problems and antioxidant use. This study exhibit mean Hcy in subjects of diabetes type 2 with tenure of less than 5 years was significantly raised as compared to normal controls. Hcy plasma levels showed significant relationship with duration of diabetes but more obvious when diabetes exceeds 5 – 10 and more than10 years.

Plasma Hcy level has supposed to be associated with vascular complications.[21] Hyper homocytenemia is linked with coronary incidents[22] and nephropathy.[23] There are variable results about high plasma levels,[20] unaltered[24] and reduced[25] in DMT2. Findings in this study is according to the study of Erh-jungHuanga et al.[26] Buysschaert et al[24] have demonstrated that Subjects with reported macroangiopathy had higher levels, our results are in accordance with findings where tHcy were higher in the diabetics.[27]

Plasma tHcy is considered as risk factor for long time in various research articles for atherosclerotic vascular disease. So our results support all this because with long duration complications of DM increases and so does Hcy. Increase NOX (NADPH oxidase) activity was observed in DM which also causes ROS formation which results in oxidative stress in diabetic patients.

Hcy-mediated vascular injury mechanism has not yet been established however in oxidative damage as Hcy can undergo auto oxidation to form various reactiveoxygen species[28], also associated with increase oxidative status in DM.[31]

High Hcy can lead to atherosclerosis by numerous processes, such as endothelial dysfunction, oxidative stress, inflammation and thrombosis.[29] Hcy has also been shown to decrease the activity of glutathione peroxidase[30] prothrombotic by the action of Hcy on various coagulation factors[32] Aggregates formed by Hcythiolactone is also intruded into cellular and secretory proteins through lysine homocysteinylation, leading to the dysfunctional proteins.

Our study showed an overall reduction in the levels of zinc and TAC, in type 2 diabetics with variable duration as compared to control. These results are in consistent with Odum et al[34] and Peerapatdit et al[35], who showed a significant reduction in the levels TAC in type 2 diabetic patients compared to control group. However, Maxwell et al[36] showed that TAC of plasma was increased in patients with uncomplicated type 2 diabetes.

An inverse correlation between fasting plasma glucose and total anti-oxidant level shows that In uncontrolled Type 2 diabetics, there is a decrease antioxidant defense against oxidative stresses suggesting that increase in oxidative stresses and some deficiency in the antioxidant defense. These factors cause increase oxidativeDNA damage, leading to pancreatic beta cell dysfunction, insulin resistance and more enhanced hyperglycemia. This vicious circle is responsible for making the diabetes more deleterious.[33]

Our results showed an inverse correlation of FBS with TAC. These results are in consistent With Akinosun et al[37] and Song et al.[38] in poorly controlled Type 2 diabetics associated with a defect in antioxidant defense of the body against oxidative stress.

A good control of FBS could possibly help reduce free radical activity and probably minimize chronic complications in diabetics. Increased blood glucose was associated with rise in oxidative stresses and some deficiency in the antioxidant defense.

According to our and study done by Dominguez LJ[39] are in agreement with that the homocysteine levels rises with increase duration of diabetes in patients with type 2 DM. Earlier studies had suggested that in DM type 2 subjects with diabetic complications, there is elevated level of Hcy associated with oxidative stress regardless of resistance to insulin. It was found by other authors that type 2 diabetic patients having cardiovascular problems had higher Hcy levels than those without it.

Hcy levels were likely to rise in complications associated with diabetes mellitus(DM). With extended time period, complications of DM increases and so does Hcy. It has been demonstrated that individuals with recognized macroangiopathy have elevated homocysteine levels. Homocysteine considerably hinders Ca2+ activated K+ channel (BKCa is major role player in mediating the contraction mechanism in the muscles of the vessels) current separately in humans and rats arteries. So the abnormalities encountered in vascular diseases might be the result of decreased and damaged BKCa by increased Hcy levels. There is also an indication that generation of NO by eNOS(epithelial nitric oxide synthase) is affected and current facts indicate that Hcy reduces the

phosphorylation level of eNOS.In South Asia, the prevalence of Zn deficiencies ranges from 15~74%.[43]

Concentration of Zinc were low in all of the groups as compared to control and it decreases gradually as duration of diabetes increases while plasma levels of Hcy gradually increases with duration of diabetes.

In a study Zn-HTSM (Zn-3,4-heptanedione-bis N4 – methylthiosemicarbazonato) a zinc complex was analyzed for its mechanism against diabetes in KKA(y)type 2 diabetic mice. Zn-HTSM-leptin interaction was also studied in detail and it was also purposed that Zn-HTSM is a powerful complex against diabetes if given orally for the treatment of type 2 diabetes.[40] There is powerful interaction among transporter of zinc, cytokines and gene expression of metallo-thionine. The correlation indicate hidden relationship of zinc metabolism and inflammatory process in diabetes.[42] It has indicated that when Zinc is high in food, Zn/Fe ratio will increase which lower the probability of DMT2 in female[41] It is revealed that Hcy and zinc are inversely related. We observed that as the duration of diabetes increases Hcy level increases and zinc level decrease in long term diabetes.

Limitations of this study include the small sample and status of dietary Zn intake, which may affect influence of Zn status on Hcy levels in DMT2

CONCLUSION

It was observed that plasma levels of homocysteine were significantly higher in subjects having type2 diabetes. Moreover, It was noted that the levels of homocysteine rises with duration of diabetes. Plasma levels of zinc were reduced in diabetic patients and significantly reduced in long duration of diabetes as levels of TAC kept reducing as duration of diabetes increases.

A large population based studies are needed to further evaluate the association between elevated Homocysteine, low Zinc status in diabetes, and its risk. The levels of Total anti-oxidant capacity, gradually decrease with duration of diabetes and are associated with oxidative stress. TAC status may be taken as early marker to detect complications in diabetic type 2 patients especially of longer duration. The levels of homocysteine should be kept at low levels to prevent from diabetic complication and zinc should be supplemented to combat oxidative stress.

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