EFFECT OF TAURINE SUPPLEMENTATION ON LEVELS OF LEPTIN, ADIPONECTIN AND BIOCHEMICAL BIOMARKERS OF ALBINO RATS INDUCED DIFFERENT METABOLIC DISORDERS

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ABSTRACT

This study was aimed to investigate the effect of Taurine on albino rats with different MDs (obesity, diabetes and hypoprotein). A total of, 30 male albino rats subjected to preparatory period, and then, divided into five groups; control (C), TAU-supplementation (TS), cholesterol (Ch), diabetes (D) and hypoprotein (Hp) groups. Post-experimental period, direct blood sampling was performed to detect the levels of TAU, leptin, adiponectin and the blood biomarkers. The findings TS showed a significant elevation in levels of leptin, adiponectine and HDL, whereas, there was significant reduction in values of cholesterol, triglyceride, LDL and VLDL. For Ch group, significant increases were detected in levels of insulin, cholesterol, LDL and VLDL. The values of glucose were increased significantly among D and Ch groups. The levels of GSH and SOD increased significantly in TS group, and reduced in D and Ch groups. Correlation between TAU and liver enzymes revealed a significant decrease in ALT and AST among TS rats, and increased among the Ch and D groups. Although, the findings of total protein differed insignificantly among all study groups. Levels of creatinine and urea reduced in TS group, increased in Ch, D and Hp. The findings concluded that TAU has many advantages and can be used to improvement of body health in both diseased (obese and diabetic) and healthy individuals.

Key words: Metabolic disorder, antioxidant, diabetes, obesity, lipid profile, Iraq

Introduction

Metabolic disorders (MDs), inability to properly utilize and/or store energy, are currently receiving considerable attention due to its increasing prevalence worldwide (Després and Lemieux, 2006; Ouchi *et al*., 2011). The MDs may show several forms including lacking the enzymes and vitamins that essential to the vital chemical functions, nutritional deficiency, abnormalities in biochemical reaction, hepatic infections, disorders in pancreatic and endocrine glands and other organs (Soetan *et al*., 2010). Several hundreds of enzyme can participate in different metabolites perform this process causing a negative effects on capability of cells to serve a critically biochemical reaction involved the processing or transporting of protein, carbohydrate and lipids (De Groot *et al*., 2019). Typically, MDs are hereditary, yet most patients might be appeared healthy for week, month, or even year; however, onset of signs generally occur during stresses (Hameed *et al*., 2015).

Based upon which enzymes are disturbance, the imbalance consequence might act enough to cause a subsequently accumulation of enzyme substrates that could with high toxicity to the body (Ighodaro, 2018). Obesity, excessive accumulation of body fat, is one of the most multi-factorial chronic diseases of elevatingrate in developed regions (Alwan, 2011; Rosa *et al*., 2014). Diabetes, characterized by chronic hyperglycemia and dyslipidemia, is a wide-range disorder associated usually with cardiovascular complication, neuropathy, nephropathy and retinopathy (Hoogwerf *et al*., 2006). Disorders of protein and amino acids metabolism represent stage for inherited metabolic condition that occurs throughout particular amino acids (Handoom *et al*., 2018).

Taurine (TAU) is a non-protein amino acid present in almost all animal tissues, most abundantly as a free intracellular amino acid in human cells. Due to its unique chemical structure, TAU is involved in numerous biological and physiological functions that confer important health benefits (Kim *et al*., 2007; Wen *et al*., 2019). Leptin, a 16kDa protein that functions as a satiety factor, is secreted by adipocytes and binds to the hypothalamic leptin receptor to enhance metabolism and reduce appetite by increasing energy expenditure and decreasing energy intake (Ghantous *et al*.,2015). Adiponectinisis a type of adipkines, a protein hormone, which secreted by adipose tissue to regulate levels of glucose and to breakdown of fatty acids (Achari and Jain, 2017). Notably, the beneficial roles of TAU, leptin and/or adiponectin in the context of MDs particularly obesity and diabetes have been studied widely in many recent reports in Iraq (Kaftan and Hussain, 2015; Tahir *et al*., 2017; Aziz *et al*., 2020; Mustafa *et al*., 2020).Nonetheless, no studies were found about the effect of TAU supplementation on leptin and adiponectin, as well as, on the biochemical parameters of metabolic disordered patients.

We hypothesized that TAU supplementation can improve health body condition along with supporting the levels leptin and adiponectin. Hence, this study aimed to investigate the effect of TAU supplementation on the levels of serum leptin and adiponectin in MDs-induced rats, and to estimate the therapeutic effect of TAU on obesity, diabetes, and restricted-protein diets through measuring serum levels of biochemical parameters (lipid profile, antioxidants, glucose, insulin, creatinine and urea).

Materials and Methods

Ethical approval

This study was licensed and performed under the regulation of Department of Physiology in the College of Veterinary Medicine / University of Basrah (Basrah-Iraq), as well as by the Department of Biology, College of Science, University of Wasit (Wasit-Iraq).

Study animals

Totally, 30 adult male albino rat of 150-200 grams body

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weight, were selected to this study and subjected initially to preparation period for one week. During this period, the study animals were received sufficient amounts of high quality food (pellets) and water (tap water).

Preparation of chemicals and diets

In this study, TAU ≥98% (Sigma-Aldrich, Switzerland) was used to prepare 3% TAU. High cholesterol diet was made by adding 10% cholesterol that prepared using the pure cholesterol (Sigma-Aldrich, Switzerland). Lowered-protein diet was prepared at 3% total protein.

Experimental study period

The study animals were randomly separated into five equal groups using plastic cages (15×35×50 cm). These groups include:

1. Control group (C): In which, rats were continued free to contact pellets and drenched with the normal saline (0.9%) throughout all experimentally period (2 months).
2. Taurin-supplementary group (TS): In this group, rats were fed pellets and drenched with normal saline (0.9%) for first 30 days of experimental period. In second 30 days of experimentally period, rats were drenched daily with 3% TAU.
3. Cholesterol group (Ch): In this, rats were fed enriched-cholesterol diet only for the first 30 days of experimental period, and then drenched daily with 3% TAU for the second 30 days of experimentally period.
4. Diabetes group (D): In which, rats were fed pellets and drenched with the normal saline (0.9%) for the first 25 days of experimentally period, and then, injected with Streptozotocin (STZ) at a daily dose 50 mg/kg for 5 days. In the second 30 days of experimental period, rats of this group were drenched daily with 3% TAU.
5. Hypoprotein group (Hp): In which, rats were fed lowered-protein diet only for the first 30 days of experimentally period, and then drenched daily with 3% TAU for the second 30 days of experimental period.

During the preparation and experimental periods (from September-2019 to November-2019), study rats were kept at room temperature (22-29ºC) and exposed daily to 12 hr light.

Blood sampling

Under general anesthesia using chloroform, totally 3-5 ml of blood were drained directly from heart by cardiac puncture using the disposable plastic syringe. Following the manufacturer instructions of each sandwich ELISA's kit (Bio Vision, USA), blood samples were tested to estimate the level of leptin, adiponectin, insulin, glucose, lipid profile [cholesterol and triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very-low-density lipoprotein (VLDL)], antioxidants [glutathione (GSH) and superoxide dismutase (SOD)], as well as the liver [aspartate transaminase (AST) and alanine transaminase (ALT)] and kidney (total protein, creatinine and urea) functions.

Statistical analysis

All obtained data documented, analyzed and figured using the Microsoft Office Excel (2013) as well as the Graph Pad Prism (6.01). Two way Analysis of Variance (ANOVA) was used to detect differences in values of serum parameters between study groups. Variation considered significant at P<0.05. The data were expressed as Mean ± Standard Deviation (M±SD), while significant differences between study groups were appeared as (*), (**), (***) and (****) for P<0.05, P<0.01, P<0.001 and P<0.0001, respectively.

Results and Discussion

Effect of TAU on leptin and adiponectine

To test whether TAU improves leptin and adiponectin, the findings showed a significant variation (P<0.05) in their values. Significantly, higher concentration of leptin and adiponectine was detected in TS group (10.03±1.19 and 25.52±1.09, respectively), while lower concentration of both parameter was reported in D group (2.76±0.09 and 8.39±), (Fig. 1).

Effect of TAU on insulin and glucose

In this study, significant increases (P<0.05) in levels of insulin were observed in Ch group (30.01±1.04) when compared to other study groups [TS (18.95±1.2), D (17.66±1.18) and Hp (20.44±0.84)] that showed no significant differences (P≤0.072) between their values (M±SD). For glucose, insignificant variation (P≤0.056) was detected between values (M±SD) of D (234.45±5.33) and Ch (185.88±2.78) groups; however, these groups revealed significantly higher values when compared to other study, TS (137.22±1.93) and Hp (150.24±2.91) groups (Fig. 2).

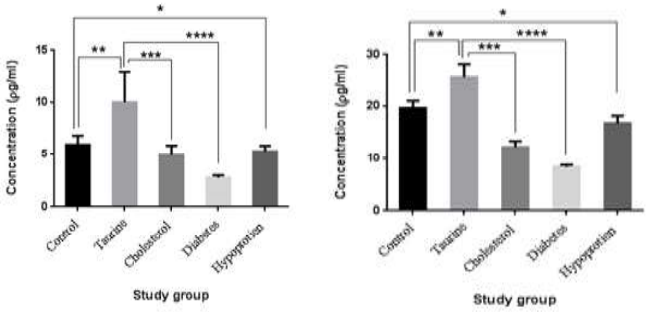

Fig.1: Results of leptin (left) and adiponectine (right) among all study groups

Effect of TAU on lipid profile

In attempt to explain differences in levels of lipid profile due to TAU supplementation, the concentration of cholesterol was increased significantly(P£0.033) in Ch (224.38±2.73) group and decreased significantly in TS (79.75±1.71) and Hp (85.51±1) groups. Regarding triglyceride, significant reduction was seen in TS (78.47±2.65) group; however, no significant differences (P≤0.064) were detected between the values of Ch (97.32±2.38), D (97.72±3.32) and Hp (95.49±1.52) groups. The findings of LDL were reduced significantly (P≤0.039) in TS (87.67±1.71) group comparing to other study groups; Ch (140.79±3.26), D (131.45±5.28) and Hp (145.79±1.56). For HDL, the findings revealed a significant increase (P≤0.023) in values (M±SD) of TS (61.51±2.08). Although, no significant differences (P≤0.085) were reported between the values of Ch (36.89±2.21), D (40.95±1.68) and Hp (41.19±1.07), all these groups were showed a significant reduction in comparison with the C (49.51±0.95) group. Levels of serum VLDL were significantly (P≤0.019) decreased in TS (15.37±0.3) group and increased in Ch (29.21±0.56) group; while, values (M±SD)

of D (20.79±0.65) and Hp (22.09±0.64) groups were differed insignificantly (P≤0.053) (Fig. 3).

Effect of TAU on antioxidants

To confirm that TAU enhanced antioxidants in MDs-exposed rats, GSH and SOD levels were measured (Fig. 4). The findings revealed that there were significant increases (P≤0.029) in values (M±SD) of GSH in TS (1.047±0.052) group and significant decreases in D (0.468±0.012) followed by Ch (0.6±0.028) but not in Hp (0.807±0.041) groups. For SOD, though the results of TS (0.58±0.014) group were increased significantly (P≤0.025), no significant differences (P≤0.074) were reported among the values (M±SD) of Ch (0.31±0.033),

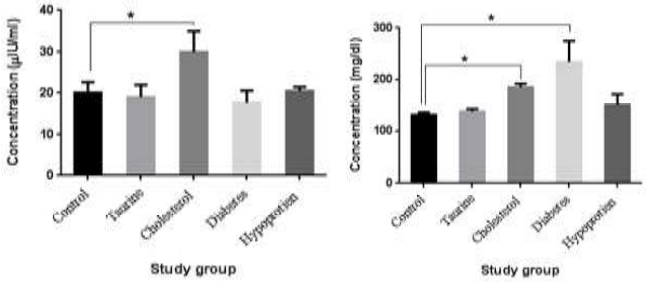

Fig. 2: Results of insulin (left) and glucose (right) among all study groups

D (0.307±0.01) and Hp (0.31±0.019) groups.

Effect of TAU on liver and kidney functions

Correlation between TAU and liver enzymes was estimated in the current study revealing a significant variation in their values (M±SD). Significantly, the findings of ALT were decreased in TS (31.26±0.87) group and increased in Ch (85.09±1.63) and D (81.02±1.6) groups. For AST, significant decreases (P≤0.017) were observed in TS (49.84±1.73) group, while significant elevation was reported in Ch (91.11±0.7) and D (89.83±1.48) groups.

Although, the findings of total protein were showed insignificant variation (P≤0.074) in their values [TS (6.89±0.21), Ch (6.56±0.22), D (6.7±0.19) and Hp (6.55±0.06)], other parameters of kidney function were recorded significant differences (P<0.05) in their values (M±SD). The measurement of serum creatinine was revealed a significant reduction in values of TS (0.59±0.01) group comparing with C (0.74±0.02), while significant increase (P≤0.043) was seen in values (M±SD) of Ch (1.13±0.14), D (1.07±0.08) and Hp (0.87±0.02). Significant, higher levels of urea were observed in Ch (46.21±2.65) and D (38.21±0.47) groups in comparison with the C (25.75±0.76) group while lower level was detected in TS (19.83±0.5) group (P≤0.024), (Fig. 5).

Certain MDs appear with variable severity, and the mild end of each disorder could be manifested by the cognitive disability and subtle feature. Obesity, diabetes and restricted-protein diets are common MDs, in which, the individuals have the inability to properly utilize and/or store energy (Huynh *et al*., 2016; Chen *et al*., 2019). In many MDs, TAU or combining of TAU with other drugs has several beneficial roles for repairing the affected organs, as well acting as promoters for balancing metabolism of energy (Wen *et al*., 2019). Our findings revealed that TAU supplementation enhance effectively the concentration

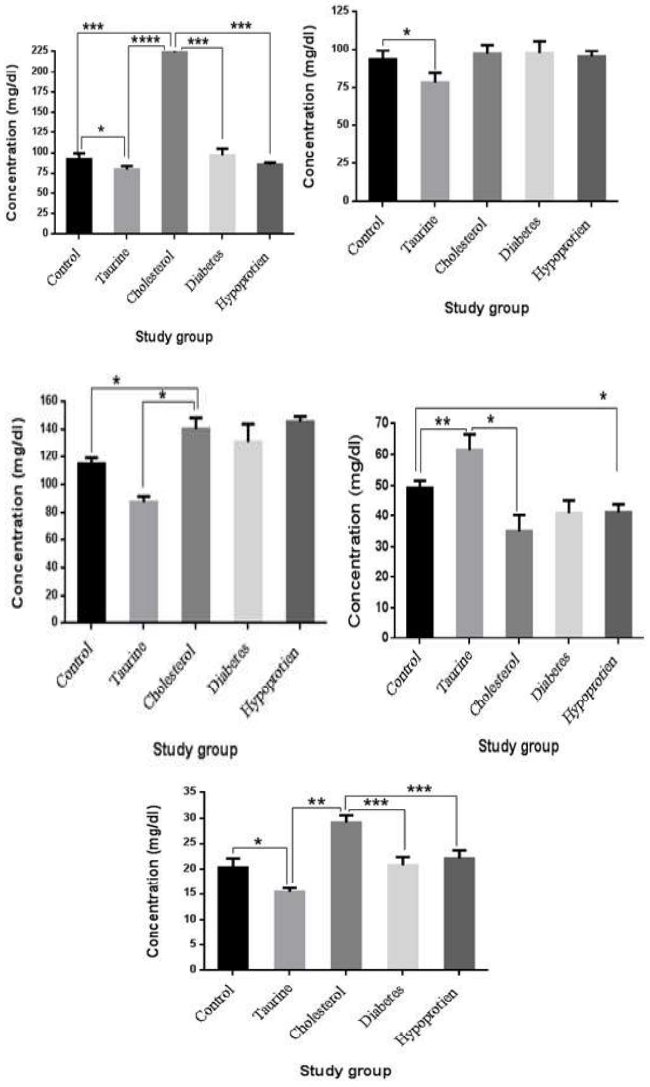

Fig. 3: Results of lipid profiles; cholesterol (upper left), triglyceride (upper right), LDL (middle left), HDL (middle right) and VLDL (lower left) among all study groups.

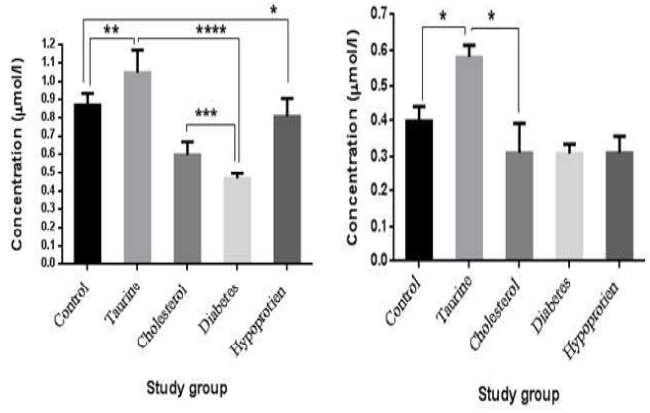

Fig. 4: Results of antioxidants, GSH (left) and SOD (right)among all study groups.

of serum leptin and adiponectin. The positive correlation between TAU and leptin or adiponectin had been confirmed by several studies (You *et al*., 2013; Abdel-Moneim *et al*., 2015; Kim *et al*., 2019). Camargo *et al*. (2015) demonstrated that TAU could modulate gene expression of leptin for suppressing neuropeptides in hypothalamus, that decrease food intakes through reduction hypothalamic resistance to leptin. Prevention of daily plasma leptin disruption caused by the high fat diet was confirmed (Figueroa *et al*., 2016). Regarding adiponectin, Chen *et al*. (2009) found that TAU supplementation could improve expression the circulating adiponectin through prevention ethanol-induced oxidative stress and attenuated tumor necrosis factor expression and steatosis, in part, by increasing expression of genes involved in fatty acid oxidation. It has been proposed that the increased levels of leptin and adiponectin can increase insulin sensitivity, which is essential to management of obesity-related diseases (Yamauchi *et al*., 2001; Matsuzawa *et al*., 2004). Kim *et al*. (2012) detected that TAU significantly reduces serum leptin but not adiponectin levels. However, Tsuboyama-Kasaoka *et al*. (2006) observed that dietary TAU supplementation increased the blood TAU concentration and prevented obesity with induction of resting energy expenditure and of gene expression involved in energy metabolism in white adipose tissue.

This study found that insulin and glucose increased significantly among Ch and D (only glucose) and decreased in TS group. In human, Brøns *et al*. (2004) showed that daily supplementation of TAU to diabetic patients, for 8 weeks, had no effect on insulin secretion or sensitivity. In animals, Kim *et al*. (2012) concluded that the feeding of rats with TAU was revealed in a significant reduction in blood glucose levels and insulin resistance but, did not improve b-cell function or islet mass. Ito *et al*. (2014) indicated that TAU is essential to functions of β-cells; thus, for preventing is lets TAU contents through TAU intakes might being the best scheme to prevent the diabetes because disorders of islet β-cells. Later, Ito *et al*. (2015) concluded that TAU deficiencies can result in many disorders concerned to metabolism of glucose, proposing that TAU can play great roles for maintaining the normal production of energy required for metabolism. Based on some experimentally as well as clinically studies, excess body weight and insulin resistance appear to associate with decreasing the concentration of TAU (Tsuboyama-Kasaoka *et al*., 2006; You *et al*., 2013; Sak *et al*., 2019). Haidari *et al*. (2020) mentioned that TAU regulates the hyper glycemia state through reducing insulin hypersecretion and elevation the sensitivity of insulin by activating adiponectin. Importantly, Yamori *et al*. (2009) reported that the urinary excretion of TAU might correlate inversely to mortalities due to infection with heart ischemia. This result indicates that TAU is greatly important for preventing the diseases related with lifestyle.

Present findings showed the administration of TAU significantly decreases the concentration of cholesterol, triglyceride, LDL and VLDL, and significant increases in concentration of HDL. Different studies have been resulted the effect of TAU supplementation in significantly decreases the serum levels of lipids such as cholesterol, triglyceride, HDL and LDL (Nandhini *et al*., 2002; Chen *et al*., 2012; Kim *et al*., 2012; Zeng *et al*., 2012). It has been reported that a high fat diet cause a decrease in blood and adipose TAU content, which is assumed to relate to the development of obesity (Ito *et al*., 2015). In a previous study (Matsushima *et al*., 2003), the findings showed that supplementation of TAU for extreme hyperlipidemic mice increased the serum HDL but did not affect serum total cholesterol, VLDL and LDL. In mice, several studies have resulted that the administration of 1% TAU to the drinking water was reduced the serum LDL and VLDL cholesterol, and increased the serum HDL (Kamata *et al*., 1996; Murakami *et al*., 1998; Chen *et al*., 2004). Choi and Chang (2009) reported that the concentration of plasma total cholesterol and triglyceride were lower in TAU, while the HDL and LDL levels were not reduced. However, the benefits of TAU on lipid metabolism in humans occur through effective decreasing of body weight, suggesting that TAU may be helpful for improving lipid metabolism in obese people, and therefore, play a role in cardiovascular disease prevention (Zhang *et al*., 2004).

Oxidative stresses and production of free radicals appeared to act great roles in beginning and developing of MDs. Recently, the members of antioxidant gain low attention. The GSH and SOD appear to be more pharmacological activity for prophylactically and therapeutically roles throughout many clinical abnormalities (Elshama *et al*., 2018; Khurana *et al*., 2018; Kassem *et al*., 2020). Evidences suggested that TAU might has an essentiallu amino acids in disease related to elevated oxidative stresses and inflammations (Lourenco and Camilo, 2002; Imae *et al*., 2014). In this study, the potent characteristics of TAU as an antioxidant were further related to elevated concentration of antioxidant enzymatic activities. Though mechanism by which TAU can affect on antioxidants still unknown, scaveng of reactive oxygen species (ROS), interfering with activity of ROS, and re-generation of thiol group might be the great likely mechanism (Imae *et al*., 2014). In a study on sulfur containing amino acids (Benedetti *et al*., 1991) and in another study on cyclosporine-A induced oxidative stress (Hagar, 2004), it has been pointed out that TAU increased the GSH levels as a result of directing more amount of cystine into GSH biosynthesis. Miyazaki *et al*. (2004) reported that administration of TAU increased GSH levels in rats due to the inhibition of GSH oxidation to prolong the exercise performance. Çetiner *et al*. (2005) reported that TAU does not have known direct effect on GSH biosynthesis but it reduces the consumption of GSH by inhibiting reactions of LPO, a marker for free radical induced damage. Sinha *et al*. (2008) have shown that TAU increased the GSH levels by inhibiting the lipid peroxidation. The increasing concentration of SOD in responding for TAU supplementation was confirmed by many studies (Nonaka *et al*., 2001; Higuchi *et al*., 2012; Choi and Jung, 2017).

Clinically, the ALT and AST levels in the plasma represent biomarkers for liver function (Lalisang and Suryaatmadja, 2012). Present study findings revealed a significant elevation in levels of ALT and AST in the groups of Ch and D suggesting an injury to the liver; and significant reduction of both enzymes in TS group suggesting TAU exerts strong protective effects in liver due to its antioxidant characteristics of TAU (Higuchi *et al*., 2012; Budhram *et al*., 2013). In a study carried out previously, significant high levels of liver enzymes in chronically infected patients with hepatitis were decreased significantly at the end of three months treatment suggesting that TAU may ameliorate

liver injury for chronic hepatitis patients (Hu *et al*., 2008). Liu *et al*. (2017) demonstrated that TAU pretreatment by intravenous injection reduced the activity of plasma ALT and AST. Król *et al*. (2020) showed that TAU supplementation normalized the level of ALT but not AST enzyme. In mammals, kidney is responsible for TAU homeostasis; however, excretion rate depends on dietary intake (Chesney *et al*., 2010). TAU participates in a number of different physiologic and biologic processes in the kidney, often reflected by urinary excretion patterns. In current study, the findings revealed a significant reduction in TAU concentration in TS group, and an elevation in Ch and D groups. Also, we showed that the concentration of total protein does not altered significantly. Michalk *et al*. (2003) detected that creatinine levels in ischemic rats were much lower than in control animals that did not receive TAU. Sagara *et al*. (2015) showed that the excretion of high TAU and lower creatinine was associated with lower risk factors. Alhumaidha *et al*. (2016) detected that the administration of TAU attenuated the toxicity-evoked disturbances including elevated serum activities of craetinine and blood nitrogen urea.

Conclusion

It was found that TAU can be used to correct MDs, and improve the body health particularly among the MDs (obese and diabetic) patients. TAU might have potential benefits in preventing or reducing the complications of MDs. Eventually, TAU could ameliorate leptin, adiponectin, lipid profile, hyperglycemia, liver and kidney functions. However, further investigations are necessary to confirm the optimal dose of TAU and assessment of negative impacts of frequent TAU supplement. Several limitations have been observed in present study including small sample size, short period of study, prior- and post-treatment evaluation of hyperlipidemic, hyperglycemic, and hypo proteinaceous groups. Concentration of TAU in urine was not determined.

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