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To study the effect of taurine on the effects of vital bones and regulate the level of glucose in type II diabetes

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ABSTRACT

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Diabetic patients, Osteocalcin, Glycemic control

Taurine is sulfur containing semi-essential amino acid that has important roles in many biological processes, but its effect on glucose homeostasis, weight, growth and bone mineralization weren’t well deϑined. Objectives: the evaluation of oral Taurine effects has used for 3 months on bone mineraliza- tion biomarker, glycemic control and body weight in type ll diabetic patients. Methods: the interventional double-blind placebo-controlled study in which

80 patients with type 2 diabetes mellitus (age range 45-55) assigned in either control (n=40), or study group the (n=40) group. The last group has received a 1000mg capsule of Taurine once a day for three months. Parameters mea- sured were serum calcium, 25(OH) vitamin D and osteocalcin, NTX-1 HbA1C% with fasting blood glucose before and after 3 months. Results: taurine led to signiϑicant (p<0.05) rise in osteocalcin, signiϑicant lowering in body weight, BMI and there were no signiϑicant changes in serum calcium, NTX-1, Vitamin D, HbA1C and fasting blood glucose, all as compared with the control value. Conclusions: the 3 months of oral Taurine are used in type II diabetic patients may modulate bone mineralization represented by elevation of osteocalcin and reduction of body weight, but has no signiϑicant effect on glycemic con- trol and did not reduce HbA1C%.

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**INTRODUCTION** 13

Diabetes Mellitus is a pandemic metabolic health 14 disturbance, which featuring by chronic hyper- 15 glycemia and induces many pathological complica- 16 tions among both sexes in a wide range of ages, so 17 these complications include microvascular compli- 18 cations like nephropathy, retinopathy, neuropathy 19 and macrovascular complications like acute coro- 20 nary syndrome and stroke. Several studies in recent 21 years approved that patients with type II diabetes 22 mellitus are prone to osteoporosis, and they are at a 23 greater risk of developing bone fragility (Oei *et al.*, 24

25 2015). A main mechanism of osteoporosis is an

26 imbalance between the activity of osteoblasts that

27 form bone, and osteoclasts that breakdown bone

28 leading to bone microstructure deterioration and

29 fractures. The other mechanisms by which diabetes

30 affect bone include hyperglycemia, oxidative stress

31 and gathering of advanced glycation end reproduc-

32 ers (AGEs) (Dede *et al.*, 2014; Dhaliwal *et al.*, 2014;

33 Rubin, 2015; Jang *et al.*, 2011). The uncontrolled

34 blood glucose level in typeII, diabetic patients can

35 affect bone metabolism, and its fragility directly or

36 indirectly leading to change in the level of bone bio-

37 chemical markers in blood or urine. The most sensi-

38 tive markers include osteocalcin (OC), the bone for-

39 mation marker measured in serum, other biomark-

40 ers can be recommended is N-terminal telopeptide

41 (NTX) as a reference marker for bone resorption.

42 The antidiabetic medications have variable effects

43 on bone metabolism, maybe a positive or negative

44 impact. The most known biguanide is Metformin,

45 because it has a positive effect on osteogenesis, via

46 activation of osteoblast-speciϑic Runx2(run–related

47 transcription factor 2). And the activation of AMP-

48 activated protein kinase (Molinuevo *et al.*, 2010;

49 Schuller-Levis and Park, 2003; Hansen, 2001).

50 At the same time, it has a negative effect on the

51 differentiation of osteoclast. Taurine is a semi-

52 essential or conditional amino acid, which found in

53 a large amount of human and animal tissues, but

54 its endogenous production is insufϑicient. Therefore

55 it must be provided by the diet or given as a sup-

56 plement. The Taurine exhibit antioxidant and anti-

57 inϑlammatory actions, as well as have many beneϑi-

58 cial roles in diabetes because it is able to block tox-

59 icity, which caused by oxidative stress, it also has a

60 role in osmoregulation, in counteracting inϑlamma-

61 tion and glucose homeostasis. The novelty of this

62 study is that the effects of taurine 1000 mg orally

63 for glycemic control, bone mineralization, and body

64 weight have not measured in human patients be-

and ethical committees in the college of pharmacy 77

and hospital. 78

**Patients Selection** 79

**Inclusion Criteria** 80

Inclusion Criteria: adult patient with age range 45- 81

55 years old, diagnosed with Diabetes Mellitus type 82

2, and each patient used medical diabetes, treatment 83

no more than ϑive years. 84

**Exclusion criteria** 85

Diseases are included malignancy, thyroid prob- 86 lems, parathyroid, pregnancy or breastfeeding, 87 medications use like vitamin D calcium supple- 88 ments, and obesity medications or blends, steroids, 89 bisphosphonates and insulin at least one month be- 90 fore starting study and to the next 3 months of 91 study, (Alkholiϑi and Albers, 2015; Arrieta *et al.*, 92

2014). 93

**Sample size determination** 94

Was determined by using by G power V3.1 software 95 assuming 1:1 subject division (control: study). The 96 response within each subject group was normally 97 distributed with standard deviation 5. If the true 98 difference in the study and control means is 5, we 99 will at least need to study 40 subjects for the study, 100 and 40 control subjects to be able to reject the null 101 hypothesis that the means of the study and control 102 groups are equal with probability (power ) 0.82. The 103 type I error probability associated with the test of 104 this null hypothesis is 0.05 (Bai *et al.*, 2016). 105

**Study groups** 106

Each diabetic patient, that fulϑilled the requirement 107 of study, was asked to sign a written consent, then be 108 randomly allocated, by using simple randomization, 109 into either control or study group. Only 80 patients 110 have completed the study successfully. 111

*Study group:* (n=40,age 48.8+3.1years ,22 males

65 fore (Lampson *et al.*, 1983; Cherif *et al.*, 1998; Nand-

66 hini *et al.*, 2004; Ahmadian *et al.*, 2017).

112

&18 females) received Taurine 1000mg capsule ( 113

Jarrow’s formulas ) orally once daily. There was no

67 **Aims of the study**

68 The evaluation effect of oral Taurine used for 3

69 months on bone mineralization biomarker, glycemic

70 control and body weight in type II diabetic patient.

71 **MATERIALS AND METHODS**

72 **Study design**

73 Randomize, double-blind placebo-controlled study,

74 this study was carried out from October 2017 to De-

75 cember 2018 in Al-Basra General Hospital. Basra

76 city–southern Iraq. After an agreement of scientiϑic

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signiϑicant difference in average ages and male, the 115 female ratio between groups. Hospital’s pharmacist 116 informed each patient about the goals of the study 117 and function of taurine after signing of written con- 118 sent. Height of the patient was registering at the be- 119 ginning of the study, in addition to body weight and 120 body mass index was measured to each patient be- 121 fore and after 3 months (Balshaw *et al.*, 2013; Chan 122 *et al.*, 2013; Chen *et al.*, 2016; Chiang *et al.*, 2014). 123

**Sampling** 124

A venous blood sample was drawn from each 125

participant, for measuring fasting blood glucose; 126

HbA1C%; serum calcium; Osteocalcin; Serum NTX 127

**Table 1: shows the name and source of kits used to measure the parameters of the study**

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| --- | --- | --- |
| parameters | Kit | Source |
| Fasting blood glucose | Glucose Assay Kit (Colorimetric) | Cell Biolab, INC |
| Serum calcium | Calcium Assay Kit | BD Biosciences, USA |
| Osteocalcin | Osteocalcin (1-43/49) ELISA | ALPCO diagnostics |
| NTX-1 (N terminal telopep-tidase of type1 collagen) | Human Cross-linked N terminal Telopep-tides of type I collagen ELISA Kit | MyBioSource, US |
| Serum 25-OH-Vitamin D | 25-OH-Vitamin Ddirect ELISA | IBL INTERNATIONAL GMBH |

**Table 2: Demographic data of patients in the study groups. Some of data expressed as Mean** *±*

**standard deviation**

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| --- | --- | --- | --- |
|  | Control group N=40 | Study group N=40 | P values |
| Age (years) | 50.2 *±* 3.7 | 48.8 *±* 3.1 | 0.072 |
| Male: female ratio | 24:16 | 22:18 | 0.821 |
| Weight (kg) | 98 *±* 14.5 | 95.8 *±* 13.3 | 0.324 |
| Height (cm) | 172.6 *±* 7.5 | 171 *±* 6.2 | 0.326 |
| Body mass index(kg/m2) | 33.1 *±* 5.8 | 32.9 *±* 5.1 | 0.821 |
| Obesity ratio | 30 (75%) | 28 (70%) | 0.802 |
| Fasting Blood glu-cose (mg/dl) | 121.5 *±* 9.8 | 122.6 *±* 12.2 | 0.544 |
| HbA1c% | 7.3 *±* 0.6 | 7.5 *±* 0.6 | 0.168 |
| Diabetes duration | 2.7 *±* 1.7 | 3.1 *±* 1.6 | 0.342 |
| (years) |  |  |  |

P val-

ues<0.05 consid- ered as signif- icant values

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(N- terminal telopeptide); 25-(OH)Vitamin D level; before and three months after administration their assigned supplement. Table 1 as follows,

**Data Analysis**

**RESULTS AND DISCUSSION** 142

**Demographic data of patients** (Czajka and Malik, 143

2016; Silva *et al.*, 2014; Luca *et al.*, 2015; Froger *et al.*, 144

2014)

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Data analyzed by using MedCalc® software V12, the

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As in Table 2 There were no signiϑicant (p<0.05) dif- 146

ferences between control and study group. In age

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data were expressed as mean + standard deviation. One – way ANOVA was used to ϑind the signiϑicant

(50.2 *±* 3.7 Vs. 48.8 *±* 3.1; p value= 0.072); male:

female ratio (24:16 for control Vs. 22:18 for study;

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p value =0.821); weight (kgs) (98 *±* 14.5 Vs. 95.8 *±* 150

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(p<0.05) effects between the groups.

13.3 ; p value=0.324); Height (cm) (172.6 *±*

7.5 Vs.

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The independent sample t-test was used to the com- parison between groups and paired t-test, was used to ϑind the signiϑicant difference between pre-and af- ter treatment values within each group, p-value <

0.05 was considered as signiϑicant (Coughlan *et al.*,

2016).

171 *±* 6.2 ; p value =0.326 ), Body mass index (33.1 152

*±* 5.8 Vs. 32.9 *±* 5.1; p value = 0.821); obesity ratio ( 153

75% control Vs. 70% study. p value = 0.802); fasting 154

Blood glucose (121.5 *±* 9.8 for control Vs. 122.6 *±* 155

12.2 for study group; p value= 0.544), Glycosylated 156

hemoglobin (HbA1C%) (7.3 *±* 0.6 for control Vs. 7.5 157

*±* 0.6 for study group; p value= 0.168) and diabetes 158

**Table 3: Comparison of bone mineralization biomarkers in both study groups; before and after treatment. Values are expressed as Mean** *±* **standard deviation.**

Control group N=40 Study group N=40 P values

Baseline After treatment Baseline After treatment

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Osteocalcin(ng/ml) | 17.4 *±* 5.6 | 18.3 *±* 5.9 | 17.7 *±* 12.3 | 28.9 *±* 10.7\*a | 0.00002 |
| Serum Vit. D(ng/ml) | 19 *±* 5.3 | 20.3 *±* 5.4\* | 18.8 *±* 6.7 | 20.8 *±* 6.8\* | 0.378 |
| Serum Calcium(mg/dl) | 7.1 *±* 2 | 7.3 *±* 1.9 | 7.1 *±* 2.1 | 7.6 *±* 2.5\* | 0.695 |
| NTX-1 (ng/ml)P val- | 20.4 *±* 7.1 | 20 *±* 6.8 | 20 *±* 8.9 | 18.3 *±* 7.6 | 0.605 |
| ues<0.05 |  |
| consid- |
| ered as |
| signif- |
| icant |
| values |
| \*signiϑicant |
| (p<0.05) |
| as com- |
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to its

base- line values

a- sig- niϑicant (p<0.05) as com- pared

to con- trol value

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duration in years (2.7 *±* 1.7 for control Vs. 3.1 *±* 1.6 for study group; p value= 0.342)

**Bone mineralization biomarkers** (Furukawa

*et al.*, 2014; Ginguay *et al.*, 2016; Ito *et al.*, 2012)

*Osteocalcin* raised signiϑicantly (p<0.05) in the study group after using Taurine for 3 months, as com- pared with its baseline value (28.9*±*10 .7) after treatment vs. 17.7*±*12.3 to baseline, also it was sig- niϑicantly (p<0,05) higher than the values of control group (28.9*±*10.7) after treatment to study group vs. 18.3*±*5.9 to control, as in Table 3.

Serum Vitamin D elevated signiϑicantly (p<0.05) in the study group, after using Taurine for 3 months as compared with its baseline value (20.8+6.8) af- ter treatment vs. 18.8*±*6.7 to baseline, this elevation was not signiϑicant (p<0.05) as compared to control value (20.8*±*6.8) to study vs. 20.3*±*1.9 to control ,as

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| in Table 3. | 176 |
| Serum calcium: elevated signiϑicantly (p<0.05) in | 177 |
| the study group, after using Taurine for 3months | 178 |
| as compared with its baseline value (7.6+2.5) af- | 179 |
| ter treatment vs. 7.1+2.1 to baseline, this elevation | 180 |
| was not signiϑicant (p<0.05) as compared to control | 181 |
| value (7.6*±*2.5) to study vs 7.3*±*1.9 to control, as in | 182 |
| Table 3. | 183 |
| N- terminal telopeptide (NTX-1) was not signiϑi- | 184 |
| cantly(p<0.05) changed in both groups, even after | 185 |
| treatment. As in Table 3. | 186 |
| **Glycemic control markers** (Hernández-Benítez | 187 |
| *et al.*, 2012; Chen *et al.*, 2012; Jong *et al.*, 2012; Locke | 188 |
| *et al.*, 2011) | 189 |
| Fasting Blood glucose was not signiϑicantly(p<0.05) | 190 |
| changed in both groups, even after treatment as in | 191 |
| Table 4 . | 192 |

**Table 4: Comparison of changes in the percentage of glycemic control parameters in both study groups. Values are expressed as Mean** *±* **standard deviation.**

Control group N=40 Study group N=40 P values

% change Fasting Blood

Glucose

-0.4 *±* 15.2 -0.2 *±* 2.2 0.934

% HbA1c 1.1 *±* 7.4 -1.5 *±* 10.7 0.211

P values<0.05 considered as signiϑicant values

**Table 5: Comparison of percentage changes in Body weight & BMI for both study groups. Values are expressed as Mean** *±* **standard deviation.**

Control group N=40 Study group N=40 P values

% change in Weight (kg) 0.43 *±* 5.8 -2.5 *±* 4.3 0.014

% change in BMI 0.41 *±* 5.8 -2.4 *±* 4.1 0.015

P values<0.05 considered as signiϑicant values

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Glycosylated haemoglobin (HbA1*C* %) was not sig- niϑicantly(p<0.05) changed in both groups even af- ter treatment, As in Table 4.

**Effect on body weight** (Junyent *et al.*, 2011; Zulli,

2011)

*The per cent change in body weight* was lowered sig-

level in the blood of Taurine treated group, that re- 228 ϑlected as signiϑicant rising as compared to control 229 group (Kinney, 2005). 230

Taurine may enhance the intestinal absorption of 231 fat-soluble vitamins, like vitamin D and studies 232 found low Taurine dietary intake may compro-

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niϑicantly (p<0.05), in the study group after using

Taurine for 3 months, as compared with a control

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mise vitamin D absorption.in this study, Taurine 234

supplement did signiϑicantly enhance intestinal ab-

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value (-2.5*±*4.3 to study vs. 0.43*±*5.8 to control ).

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sorption of vitamin D, so that serum level of 25 236

(hydroxy) Vitamin D, was elevated signiϑicantly

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and same to body mass index was (-2.4*±*4.3 to study

vs 0.41*±*5.8 to control), as in Table 5.

in group used Taurine but unfortunately, these changes were not signiϑicant as compared to the

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Taurine contains the sulfur amino acid, that avail-

able in mammalian tissues. A lot of studies are

control group (Udawatte *et al.*, 2008). 240

Serum calcium changes in this study were parallel to

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talked about its function, and roles in many known biological processes, e.g. calcium metabolism, pro-

changes in vitamin D level.

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tein phosphorylation, energy extraction …..etc. De- spite the importance of Taurine in these biological functions, its interaction in the regulation of glucose homeostasis, weight, growth and bone metabolism remain not well deϑined.

In this study, Taurine supplement used for 3 months,

In addition to that; blood N-terminal telopeptide, a 243

bone resorption biomarker, that secreted by the ac- 244

tivity of osteoclasts, was not signiϑicantly changed by 245

Taurine supplement. This may indicate that Taurine 246 may not stimulate osteoclast, probably not enhance 247 bone turnover activities. The serum calcium was not 248 also changed signiϑicantly, as compared to the con-

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in type 2 diabetic patients and used to study its ef-

fect on biochemical markers related to bones min-

trol group (Choi and Seo, 2013; Yuan *et al.*, 2006).

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eralization, diabetes control and effect on body weight (Puerta *et al.*, 2010).

Taurine administration as a supplement was able to raise the serum level of osteocalcin signiϑi- cantly(p<0.05), as in Table 3. this ϑinding was differ- ent from results of many studies, that found the use of Taurine have not resulted in signiϑicant change, in the level of osteocalcin.

Taurine stimulates osteoblasts resulted in secreting osteocalcin. Due to oral supplementation, taurine probably was available in blood in sufϑicient con- centration, to produce sustain raise in osteocalcin

Taurine may suppress insulin secretion in nondia- 251

betic pancreatic islets and may serve as a regular fac- 252 tor to insulin secretion, and blood glucose level . en- 253 hancer to peripheral insulin sensitivity, and Taurine 254 may have a hypoglycemic effect. There were no sig- 255 niϑicant changes in the level of fasting blood glucose, 256 or HbA1C% measures during studying this in agree- 257 ment with (Zhang *et al.*, 2004) that found no signif- 258 icant change in fasting blood glucose, after 7 weeks 259 from using the Taurine supplement in non –diabetic 260 individuals. Although so, body weight and BMI in- 261 dex were signiϑicantly reduced after treatment with 262

Taurine, but this was not signiϑicant as compared to 263

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the control group. This ϑinding was in agreement with (Zhang *et al.*, 2004).

**CONCLUSIONS**

Taurine 1000 mg orally use in type II diabetic pa- tients may modulate bone mineralization repre- sented by elevation of osteocalcin, and may reduce body weight but has no signiϑicant effect on glycemic control and did not reduce HbA1C%.

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**The Contribution of authors**

We declare that this work achieved by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne to the authors. Falah Hassan Shari, Hiba Dawood and Jubran K. Hassan conceived and de- signed the study. Qais A. Aljazaeari, Mazin A.A.Najim and Ahmad Salahuddin designed all the experiments and revised the manuscript. H. N. K. AL-Salman performed the experiments, collected, analyzed the data, and wrote the manuscript.

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