

## ORIGINAL ARTICLE

**EFFECT OF TAURINE AND  $\beta$ -ALANINE ON BLOOD GLUCOSE, SERUM INSULIN, AND INSULIN RESISTANCE IN TYPE 2 DIABETIC RATS**
**Amina Rasul, Aarsal Sami\*, Ghazala Jawwad\*\*, Nadia Latif\*\*\*, Irum Rehman†, Jaleel Kamran**

Department of Physiology, Watim Medical &amp; Dental College, Rawat, \*Shifa International Hospital, Islamabad, \*\*Bahria University College of Medicine, Islamabad, \*\*\*Fazaia Medical College, Islamabad, †Margalla Institute of Health Sciences, Rawalpindi, Pakistan

**Background:** Taurine and  $\beta$ -alanine have similar structures and compete for the same transporter. The ability to retain taurine and carnosine is impaired in type 2 diabetes mellitus (T2DM). This study was carried out to compare the effect of taurine and  $\beta$ -alanine on blood sugar, serum insulin, and insulin resistance, in T2DM rats. **Methods:** This laboratory-based experimental study was conducted from Jul to Sep 2020. Ninety male Sprague Dawley rats were randomly divided into three groups, each comprising of 30 rats. All rats were fed on a taurine-free high-fat diet for 4 weeks. Rats were supplemented in drinking water, as follows: Diabetic control rats with 0.02% (w/v) taurine, diabetic  $\beta$ -alanine rats with 3% (w/v)  $\beta$ -alanine, and diabetic taurine rats with 3% (w/v) taurine. On the 14<sup>th</sup> day, a single intraperitoneal injection of low dose streptozotocin (STZ) (35 mg/Kg), was administered to all rats. On the 21<sup>st</sup> day, tail vein sampling was done to confirm the development of T2DM. On the 28<sup>th</sup> day, rats were terminally anaesthetized and intra-cardiac blood samples were used to estimate the blood sugar, serum insulin, and HOMA-IR. **Results:** Significant differences were found between the control and taurine groups, as well as the  $\beta$ -alanine and taurine groups. No significant differences were found in these parameters when control group was compared to  $\beta$ -alanine group. **Conclusion:** Taurine significantly improves glucose homeostasis in diabetic rats. Future studies should explore taurine in combination with insulin to assess potential dose-sparing effects.

**Keywords:** Beta-alanine, Diabetes mellitus, High-fat diet, Insulin resistance, Taurine

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**INTRODUCTION**

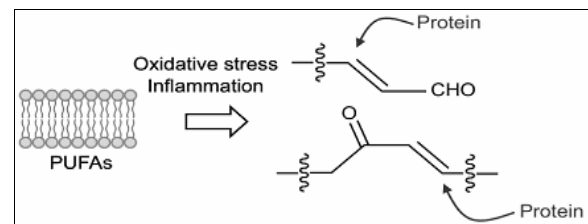
The incidence of type 2 diabetes mellitus (T2DM) continues to grow at an alarming rate. The most salient feature of T2DM is progressive damage to the  $\beta$ -cells of pancreatic islets, impaired insulin secretion, and hyperglycaemia. Sustained hyperglycaemia and hyperinsulinemia lead to  $\beta$ -cell failure.<sup>1</sup> The  $\beta$ -cell failure results primarily from glucolipotoxicity, which in turn is attributed to multiple biochemical effects, including oxidative stress (OS).<sup>2</sup>

Oxidative stress results when the cellular oxidative and antioxidant enzymes balance tips towards the former, and an excess of reactive oxygen species (ROS) is produced.<sup>1</sup> This initiates free-radical-associated oxidation of polyunsaturated fatty acids (PUFA) in lipid peroxidation (LPO) with increased synthesis of reactive carbonyl species (RCSs). The RCS reacts avidly with proteins via Michael addition (Figure-1) to generate diverse covalent adducts known as advanced lipoxidation end-products (ALEs).<sup>3,4</sup> The RCS also generates advanced glycation end-products (AGEs), and both ALEs and AGEs play a role in the pathogenesis and progression of diabetes.<sup>2,4</sup>

A vicious cycle ensues in which chronic hyperglycaemia and OS are mutually causative. Studies have reported 30% lower levels of antioxidant enzymes in the islets as compared to the liver, suggesting that the  $\beta$ -cells are especially prone to oxidative damage caused by ROS and that the protection of  $\beta$ -cells from such

damage is dependent on the inhibition of glucolipotoxicity-induced ROS generation.<sup>1</sup>

There is a need to pursue novel interventions that can alleviate oxidative and carbonyl stresses to help hinder disease progression, offer better clinical prognosis, and have minimal toxic effects.<sup>5</sup> Previous animal and human studies have demonstrated the positive impact of carnosine (CAR) and taurine (TAU), on glucose homeostasis in diabetes.<sup>1,2,5-7</sup>



**Figure-1: Michael addition in the formation of ALEs<sup>3</sup>**

Taurine, a sulphur-containing amino acid, is richly distributed endogenously and has multi-target anti-oxidant effects that significantly alleviate glucolipotoxicity induced OS and apoptosis in pancreatic islets.<sup>1,8</sup> TAU promotes insulin secretion by inhibiting the pancreatic ATP-sensitive  $K^+$  channels, and thus, plays a pivotal role in insulin homeostasis.<sup>8</sup> CAR is an endogenously distributed dipeptide synthesized from  $\beta$ -alanine (BA) and histidine. The intracellular synthesis catalyzed by carnosine synthase (CARNS 1) is rapid, though greatly limited by BA levels.<sup>6</sup> CAR is a major endogenous carbonyl scavenger that quenches RCS via

intramolecular Michael addition and can mitigate aspects of metabolic disturbances in diabetes.<sup>2</sup>

TAU and BA share the same secondary active transport mechanism via the transmembrane TAU transporter (TAUT) found in target cells, including islets'  $\beta$ -cells and skeletal muscle cells.<sup>6</sup> The activity of the TAUT decreases in diabetes, which means that the antioxidant capacity of the cells decreases.<sup>1</sup> Moreover, significantly decreased TAU and CAR levels are found in diabetic animals<sup>9,10</sup> and humans<sup>11,12</sup>, and the tissue levels of both TAU and CAR can be increased by oral supplementation.<sup>8,12</sup> This study was done to compare the effect of the two on glycaemic parameters in T2DM.

## METHODOLOGY

This laboratory-based experimental study was conducted at the Physiology Department, Army Medical College, Rawalpindi, in collaboration with the National Institute of Health (NIH), Islamabad, from Jul to Sep 2020. Approval for research was obtained from the Ethical Review Committee of the College (ID/150). Ninety healthy male Sprague Dawley rats aged 60–90 days, weighing 250±50 grams, without pre-existing diabetes (plasma glucose levels >200 mg/dL)<sup>12</sup> as tested by tail vein sampling, were selected. Rats were housed in a well-ventilated room at 22±4 °C temperature and a 12-hour light/dark cycle.

Rats were randomly divided into 3 groups: I (Control, n=30), II (BA group, n=30), and III (TAU group, n=30). For 4 weeks, all 3 groups were fed with a TAU-free-high-fat diet.<sup>13</sup> For the same duration, the groups were supplemented in their respective drinking waters, as: Group I rats with 0.02% TAU to match the TAU content of standard rat chow, Group II rats with 3% BA to reduce plasma and tissue TAU content by 50%, due to competitive inhibition of TAU uptake by TAUT, and Group III rats with 3% TAU to equal the amount of BA documented to produce maximal TAU depletion.<sup>14</sup> Animals were allowed free access to diet and drinking water.

On the 14<sup>th</sup> day, a single intraperitoneal injection of streptozotocin (STZ), in a dose of 35 mg/Kg body weight was administered in the lower right quadrant of the rats' abdomen. On the 21<sup>st</sup> day, tail vein blood sampling was done to measure plasma glucose and insulin resistance (by HOMA-IR) to establish the development of T2DM with IR, according to the criteria of a cut-off value of plasma glucose level >200 mg/dL and HOMA-IR value of >3.9.<sup>14,15</sup> On the 28<sup>th</sup> day, after prior overnight fasting, rats were sacrificed by ether anaesthesia overdose. Intracardiac blood samples were collected in sodium fluoride tubes for plasma, and in gel separator tubes for serum. The samples were centrifuged at 4,000 rpm for 15 minutes to separate plasma and serum. After centrifugation, the plasma and serum were pipetted out, put into the polypropylene storage tubes,

and stored at -80 °C for the assays of glucose and insulin, respectively. Plasma glucose was measured with glucose oxidase method, serum insulin was measured with Sandwich ELISA, and HOMA-IR was calculated from these values.

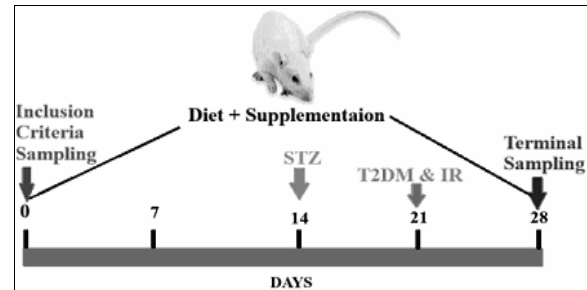


Figure-2: Experimental design

Data was analysed on SPSS-21 to calculate the Mean±SD of all variables. ANOVA was applied to determine the differences among groups. Post-hoc Tukey test was used for pair-wise comparison of groups, and  $p \leq 0.05$  was considered statistically significant.

## RESULTS

Table-1 shows the mean plasma glucose levels, serum insulin levels, and HOMA-IR values. ANOVA shows significant differences in all three glycaemic parameters among the groups ( $p < 0.001$ ).

Post hoc Tukey's test was applied to compare plasma glucose levels, serum insulin levels, and HOMA-IR between two groups to find which group significantly differed from the other. Significant differences were found in all three glycaemic parameters between the control and taurine groups. No significant differences were found in these parameters when  $\beta$ -alanine group was compared to controls. (Table-2).

Table-1: Comparison of plasma glucose, serum insulin, and HOMA-IR among control,  $\beta$ -alanine treated, and taurine treated groups, by ANOVA at the end of the study (Mean±SD)

Parameters	Control	$\beta$ -alanine	Taurine	<i>p</i>
Fasting Plasma glucose (mg/dL)	282.23±9.77	282.80±10.24	122.03±7.51	<0.001
Serum insulin ( $\mu$ U/L)	3.61±1.15	3.41±1.66	5.48±0.92	<0.001
HOMA-IR	2.53±0.83	2.37±1.14	1.65±0.30	<0.001

Table-2: Comparison of plasma glucose, serum insulin, and HOMA-IR among control,  $\beta$ -alanine treated, and taurine treated groups, by Post Hoc Tukey test at the end of the study (*p*-values)

Parameter	Control and $\beta$ -alanine	Control and taurine	$\beta$ -alanine and taurine
Fasting Plasma glucose (mg/dL)	0.969	<0.001	<0.001
Serum insulin ( $\mu$ U/L)	0.818	<0.001	<0.001
HOMA-IR	0.757	<0.001	<0.01

## DISCUSSION

The animal model used in this study closely replicates the natural history and metabolic characteristics of human T2DM. A high-fat diet induced insulin resistance (IR), while a low dose of STZ caused  $\beta$ -cell dysfunction. As compensatory hyperinsulinemia declined, it failed to counterbalance IR, leading to overt hyperglycaemia.<sup>15</sup>

Zhao *et al*<sup>1</sup> revealed that hyperglycaemia in T2DM primarily results from inadequate insulin secretion due to pancreatic  $\beta$ -cell loss, with individuals exhibiting a 30–63% reduction in  $\beta$ -cell volume compared to non-diabetic individuals. Their study showed that TAU supplementation alleviated hyperglycaemia in male rats fed a high-fat, high-glucose (HFHG) diet. This beneficial effect was attributed to TAU's antioxidant properties, specifically through activation of the nuclear factor erythroid 2 related factor 2/heme oxygenase 1 (Nrf2/HO-1) pathway. This pathway regulates cellular responses to OS by upregulating antioxidant gene expression and suppressing pro-inflammatory cytokines. Under glucolipotoxic OS induced by the HFHG diet, the protective effects of the Nrf2/HO-1 pathway were compromised, leading to severe pancreatic apoptosis. TAU supplementation mitigated this damage by enhancing antioxidant defences and suppressing OS. Compared to non-supplemented HFHG rats, TAU-supplemented HFHG rats exhibited increased Nrf2 and HO-1 activity, elevated superoxide dismutase levels, reduced malondialdehyde levels, and consequently, reduced pancreatic damage.<sup>1</sup> The animal model and TAU administration protocol used in their study were similar to ours; however, the 4-month duration of their study allowed for the detection of TAU's antioxidant effects through gene expression and protein synthesis.<sup>1</sup>

Murakami *et al*<sup>16</sup> reported that TAU had occasional but significant hypoglycaemic effects in STZ-injected C57BL/6J mice, accompanied by the upregulation of hepatic glucose transporter (GLUT-2) and UDP-glucose phosphorylase 2, suggesting that TAU improves hepatic glucose metabolism by promoting glucose uptake and glycogen synthesis. TAU's antioxidant effects were organ-specific, protecting the liver and kidney but not significantly protecting pancreatic  $\beta$ -cells or restoring insulin production.<sup>16</sup> The 3% dose of TAU, the same as in our study, was adequate to produce the initial hypoglycaemic effect in the C57BL/6J mice. Later, the OS-mediated extensive cytotoxic damage to the pancreatic tissue by the high dose of STZ (200 mg/Kg) may have overwhelmed the protective antioxidant effects of 3% TAU. Although the extent of  $\beta$ -cell destruction was not assessed in our study, the significant increase in serum insulin levels following TAU

treatment suggests that a sufficient population of functional  $\beta$ -cells remained and responded to the insulinotropic effects of TAU.

Díaz-Rizzolo *et al*<sup>7</sup> investigated the preventive effects of a sardine-enriched diet on T2DM development, using the Finnish Diabetes Risk Score. Prediabetic subjects aged >65 years consumed a sardine-based diet (200 g/week) for a year. Sardine is a source of TAU (147 mg/100 g of serving). At the end of the study, there was a decrease in levels of HbA1c and glucose, compared to the pre-intervention values. This T2DM preventive effect was attributed to improved IR secondary to increased high-density lipoproteins and adiponectin, and decreased triglycerides.<sup>7</sup> In a randomized control trial<sup>8</sup>, 8 weeks of TAU (1 g, three times per day) treatment in T2DM patients did not improve blood glucose, HbA1c, and lipid profile, despite improvement in serum insulin and HOMA-IR, and lowering of MDA and TNF levels, compared to the placebo group.<sup>8</sup> The discrepancy between the results could be due to factors such as the severity of T2DM, the dose of TAU, other medications, and the study duration.

Albrecht *et al*<sup>17</sup> reported an insulinogenic effect of CAR in BTBR ob/ob mice, a type 2 diabetes (T2D) model characterized by leptin deficiency, insulin resistance, and hyperglycaemia, which develops a phenotype similar to advanced human diabetic nephropathy (DN). Their study found a 2-fold increase in serum insulin levels, accompanied by elevated serum C-peptide levels, and a negative correlation with glycaemia. They suggested that either CAR activates the insulin-signalling cascade after internalization into the pancreas, or CAR is first hydrolyzed to beta-alanine (BA), which then opens voltage-activated L-type  $\text{Ca}^{++}$  channels, to promote insulin secretion. Although the BTBR ob/ob mouse model is useful for studying diabetic nephropathy, its leptin deficiency limits its similarity to human diabetes due to two key differences: leptin deficiency is not typical in humans with diabetes, and leptin administration can reverse the disease in these mice.<sup>18</sup>

Cripps *et al*<sup>2</sup> investigated the effects of CAR on INS-1  $\beta$ -cells, isolated from CD-1 mice and exposed to glucolipotoxic conditions. The results showed a significant increase in ROS and impaired insulin secretion. However, treatment with 1 mM and 10 mM CAR reduced ROS levels and enhanced secretagogue-stimulated insulin secretion. Notably, the higher concentration of CAR (10 mM) resulted in a nearly two-fold increase in insulin secretion compared to the lower concentration (1 mM). While INS-1 cells are a reliable  $\beta$ -cell model, they are transformed cell lines<sup>2</sup> and may not fully replicate primary  $\beta$ -cell biology. Therefore, validating these results in whole animal models is crucial to ensure physiological relevance.

In a randomized controlled trial<sup>19</sup>, CAR reduced glycaemia in 82 T2DM patients, probably by increasing insulin production from the pancreas and reducing OS. However, the patients received 2 other supplements (ALA and thiamine), hence, this effect cannot be assigned to CAR alone.<sup>19</sup>

## CONCLUSION

Our findings substantiate previous studies of the beneficial effects of TAU on glucose homeostasis and support the supplementation of TAU as an adjunct therapy in T2DM. Future studies should investigate the optimal TAU dosing and duration, synergistic effects with existing diabetes treatments, and long-term efficacy and safety in diverse patient populations.

## RECOMMENDATION

It is suggested that combined supplementation of insulin and taurine be investigated to assess whether combined therapy could be a more effective approach, that may also reduce the dose of insulin therapy in patients.

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## Address for Correspondence:

**Dr Amina Rasul**, Department of Physiology, Watim Medical & Dental College, Rawat, Pakistan. **Cell:** +92-345-8558532  
**Email:** aminasami483@gmail.com

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## Contribution of Authors:

**AR:** Concept, data acquisition, analysis, interpretation and drafting

**GJ:** Revision, approval

**IR:** Data analysis, interpretation

**AS:** Analysis, interpretation, revision and drafting

**NL:** Data analysis, interpretation and data acquisition

**JK:** Data interpretation and revision

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