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Two weeks taurine supplementation reverses endothelial dysfunction in young male type 1 diabetics

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Abstract

Type 1 diabetics have a well-recognised risk of accelerated cardiovascular disease. Even in the absence of clinical signs there are detectable abnormalities of conduit vessel function. Our group has previously reported reversal of endothelial dysfunction in diabetics with pravastatin. In young asymptomatic smokers, taurine supplementation has a beneficial impact on macrovascular function, assessed by FMD, and shows an up-regulation of nitric oxide from monocyte–endothelial cell interactions. We hypothesise that taurine supplementation reverses early endothelial abnormalities in young male type 1 diabetics, as assessed by applanation tonometry, brachial artery ultrasound and laser Doppler fluximetry. Asymptomatic, male diabetics (n=9) were scanned prior to treatment and then randomised in a double-blind cross-over fashion to receive either 2 weeks placebo or taurine. Control patients (n=10) underwent a baseline scan. Assessed diabetics had detectable, statistically significant abnormalities when compared with controls, in both arterial stiffness (augmentation index) and brachial artery reactivity (FMD). Both of these parameters were returned to control levels with 2 weeks taurine supplementation. In conclusion, 2 weeks taurine supplementation reverses early, detectable conduit vessel abnormalities in young male diabetics. This may have important implications in the long-term treatment of diabetic patients and their subsequent progression towards atherosclerotic disease.

Key words

Applanation tonometry, diabetes mellitus, flow-mediated dilatation, laser Doppler fluximetry, taurine

Introduction

In patients with type 1 diabetes, cardiac autonomic neuropathy may be present at a very early age, even in an asymptomatic population.[1] This is associated with a significant increase in mortality.[2] Several clinical trials have generated important results that validate effective strategies for modifying cardiovascular risk in diabetics.[3] Even in the clinically asymptomatic type 1 diabetic patient there are statistical differences in blood pressure.[4] These individuals have statistically higher end systolic blood pressure, even in the setting of clinically asymptomatic disease, when compared with controls. Diabetic retinopathy is considered an early sign of widespread overall vascular damage.[5] Interestingly, even in the absence of retinopathy, nephropathy and neuropathy, young assumed-asymptomatic diabetics have clinically detectable abnormalities, predictive of the development of future cardiovascular complications.[6-11] There is even evidence of cardiovascular abnormalities in diabetic children as young as 11 years.[9] Clinical assessment for nephropathy, neuropathy and retinopathy is commonplace, each reflecting both control and stage of disease. Non-invasive assessment of endothelial function in diabetics is both reproducible and reliable. Pulse wave velocity and pulse wave assessment can be determined from measurements of pulse waveform. Increased pulse wave velocity has been associated with increasing age, arterial blood pressure, diabetes, smoking and end-stage renal disease.[12] Arterial and endothelial dysfunction is different in high and low-risk subjects,[13] with arterial elasticity assessment by radial pulse waveform analysis

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correlating with FMD in young healthy subjects and older type-2 diabetics.

HMG CoA reductase inhibitors are known to reverse endothelial dysfunction in young, normoalbuminuraemic, male diabetics.[4,14] Experimental evidence suggests that HMG CoA reductase inhibitors increase both expression and activity of endothelial nitric oxide synthase,[15,16] and therefore up-regulate nitric oxide and reverse endothelial dysfunction. Lifelong statin treatment presents economical, ethical and psychological dilemmas, with a recognised incidence of adverse side effects such as muscle and liver toxicity. The incidence of transaminase increases greater than threefold is approximately 1% for all statins, and is dose related.[17] Myopathy occurs in 1 in 1000 patients.[18] Also, the risk of rhabdomyolysis and other adverse effects with statin use can be exacerbated by several factors, including diabetes.[18]

β-aminoethane sulphonic acid, or taurine, is a conditionally essential amino acid, found abundantly in tissues that are excitable and rich in membranes that generate oxidants. It is the most prevalent of all amino acids in skeletal tissue, cardiac muscles and the brain, and is essential in the functioning of the brain, heart, lungs, blood, liver, pancreas, gall bladder and the kidney. Food sources include dairy products, oatmeal and seafood. It is now well accepted that taurine has an important role to play in prevention of hypertension and stroke.[19] In diabetic patients a hypoglycaemic effect has previously been reported.[20] Several papers have reported that taurine potentiates the effect of insulin,[21] and possibly the insulin receptor.[22] In type 1 diabetics both plasma and platelet taurine levels are reduced,[23] with oral supplementation returning them to above control levels.[24, 25] Long-term treatment with taurine in streptozotocin-induced diabetic rats reduced mortality.[26] Taurine has also been shown to inhibit ischaemia-induced apoptosis in cardiac myocytes[27] and endothelial cells.[28] It protects against myocardial injury in hyperhomocysteinaemia in rats,[29] it reduces iron-mediated myocardial oxidative stress and preserves cardiovascular function in a murine model,[30] and its therapeutic role in the reduction following ischaemia/reperfusion injury is well documented.[31]

We therefore hypothesised that taurine supplementation in normoalbuminuraemic type 1 diabetics reverses early, detectable, endothelial abnormalities assessed by applanation tonometry, brachial artery ultrasound and laser Doppler fluximetry.

Methods

Patient population

Young male patients with type 1 diabetes mellitus were recruited from the diabetic day care centre at Beaumont Hospital, Dublin, Ireland, under the supervision of a Consultant Endocrinologist. All patients were male and under 30 years of age. They were all type 1 diabetics, with no evidence of macrovascular or microvascular disease and on no other medication apart from the appropriate insulin dose. All patients had a 24-h urine collection and urinary albumin excretion status to exclude microalbuminuria (Cobasmiras, Roche).

Exclusion criteria:

- Other risk factors for the development of cardiovascular disease, including smoking, hyperlipidaemia, hypertension, family history of premature vascular disease
- Female sex
- BMI>30

Control subjects underwent the same exclusion criteria. All patients were age, sex and weight matched.

Treatment protocol

All patients were provided with a thorough explanation of the study. Subjects and General Practitioners were given an information leaflet, and subjects gave informed consent to the study. The Beaumont Hospital Ethics Committee approved this study, and the Irish Medicines Board approved the use of placebo and taurine. Diabetics were supplemented with 1.5 g/day taurine (500 mg three times daily) (Twinlab) for 14 days. Placebo was an identical tablet administered three times daily for 14 days also.

Controls and diabetics were assessed at baseline. Diabetics were then randomised in a double-blind, cross-over fashion to either placebo or control and treated for 2 weeks, reassessed and treated for a further 2 weeks with the other medication and then reassessed again (Figure 1). Randomisation was achieved by placing of the tablets, placebo or taurine, in identical envelopes by an independent, non-medical member of staff. The envelopes were then labelled with numbers only, thereby not giving away identify of the treatment limb but allowing for identification of the various limbs at the end of the study. Diabetics were assessed at three separate time points, 2 weeks apart. Controls were assessed at baseline.

Haemodynamic studies

All studies were performed in the non-invasive vascular laboratory at Beaumont Hospital, Dublin, Ireland, under the supervision of a consultant in vascular imaging. All non-invasive assessments took place in a quiet, temperature-controlled room (20°C) with the subject lying comfortably in a resting supine state for 15 min. Subjects were asked to avoid caffeine and exercise for the preceeding 12 h. Blood pressure was then assessed on three occasions and the mean value, along with patient demographics, height and weight were recorded.

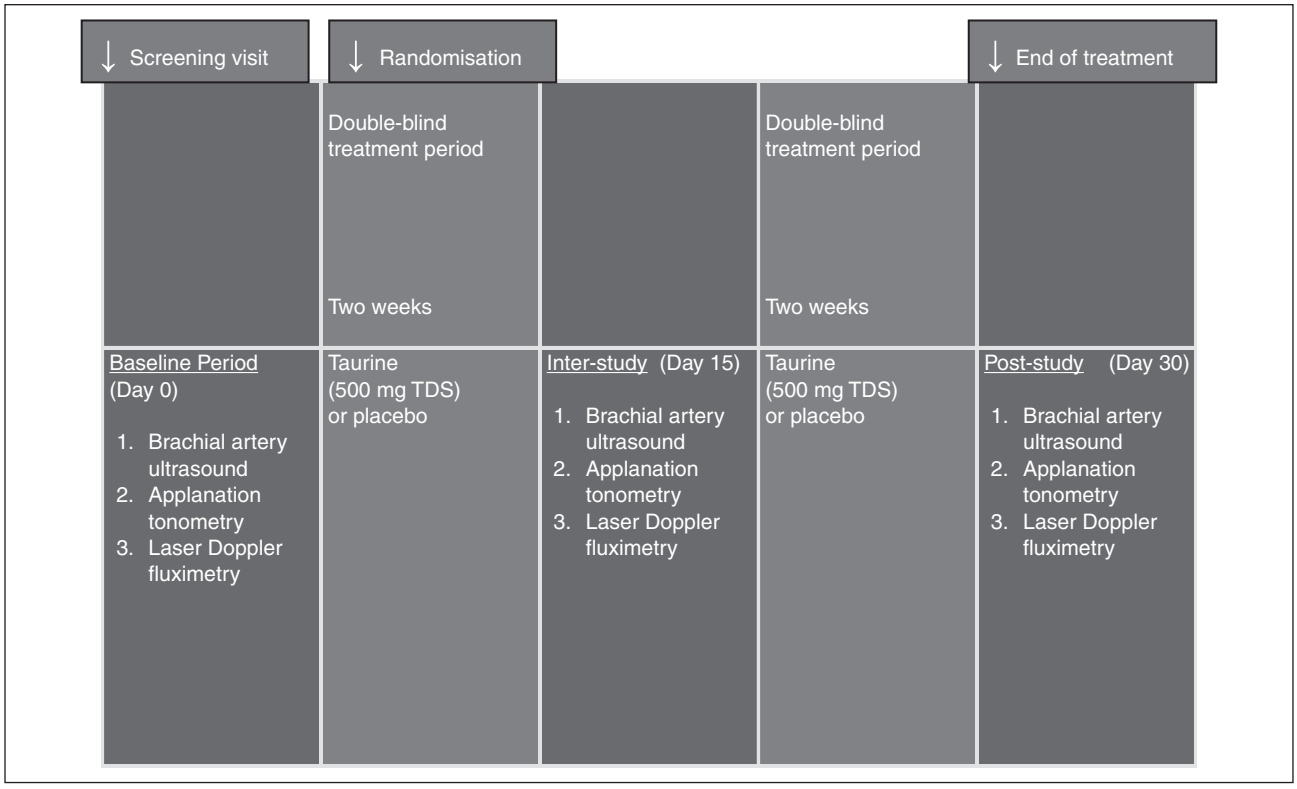

Figure 1. Study protocol for the trial.

Brachial artery ultrasound and flow-mediated dilatation

Flow-mediated changes in conduit artery diameter are caused by shear stress-induced generation of endothelial derived vasoactive mediators,[32] reflected in FMD. This technique involves measurement of the brachial artery,[33] assessed by high-resolution external vascular ultrasound in response to an increase in blood flow (causing shear stress) during reactive hyperaemia (inflation of a distal cuff placed around the wrist). This leads to endothelium-dependent dilatation; the response is then contrasted with that to sublingual GTN, an endothelium-independent dilator. The artery is therefore scanned at three time points: at baseline, immediately following reactive hyperaemia and finally after administration of GTN. A cuff inflation time of 270 s is now widely accepted to produce adequate hyperaemia for assessment of FMD.[34] This technique for assessment of endothelial function has been extensively described and is accurate and reproducible in vivo.[32,33,35-38] The brachial artery is imaged using a 13 MHz linear array transducer ultrasound system (Acuson 128XP/10 system, Acuson, California). The subject's right arm is comfortably immobilised in the extended position to allow constant imaging of the brachial artery. The artery is scanned in longitudinal section with a pulsed Doppler signal at a 70° angle to the vessel and at a location in the antecubital fossa where the clearest anterior posterior M lines are visible. Images are recorded on videotape for subsequent off-line analysis using ultrasound calipers. Baseline readings are taken for 2 min. A blood pressure cuff applied to the distal right forearm is then inflated to 240 mmHg for 4.5 min and subsequently deflated. The endothelial-dependent vasomotor responses to reactive hyperaemia are recorded 45–60 s after cuff deflation. GTN is then administered sublingually and endothelial-independent dilatation is assessed as above. At later off-line analysis the baseline brachial artery diameter, FMD in response to reactive hyperaemia and endothelial-independent dilatation are calculated. Diameter changes are expressed as the percentage change relative to the mean baseline scan (100%). Using ultrasonic calipers, measurements are taken from the anterior to the posterior M line co-incident with the end of diastole (on the ECG tracing) using the 'm' mode. The mean diameter is calculated from four cardiac cycles incident with the 'R' wave on the ECG.

Applanation tonometry – assessment of central and peripheral haemodynamics

With each beat of the left ventricle a new pulse wave is formed, each reflective and predictive of cardiac function.

Arterial tonometry permits accurate representation of the pressure waveform at sites where the artery can be compressed against underlying bone. Ideal sites are radial and carotid arteries.[39] Radial tonometry is more reproducible; it gives an accurate pressure wave contour and is a fair representation of pulse pressure. The technique is relatively simple and involves placement of a flat sensor which flattens the arterial wall, eliminating tangential pressures and exposing the artery to pressure within the artery and therefore accurately recording it. Synthesised waveforms correspond well to those recorded invasively in the ascending aorta, or to surrogate waveforms measured non-invasively.[40] The waveform is then transferred into the corresponding central arterial waveform, using a generalised transfer factor based on data from invasive recordings.[41] Therefore pulse waveform analysis can be used to record the peripheral waveform and to generate a corresponding central waveform. Both waveforms can then be analysed to give information on the augmentation index and central pressures. The augmentation index was initially described by Kelly et al.[42,43] as the ratio of augmentation index pressure (differences in pressure between early and late systolic shoulders of the pulse waveform) and pulse pressure expressed as a percentage. This is now a well-accepted technique for the assessment of arterial stiffness.[41,44-47] In this pilot clinical trial the right radial pulse was used for assessment of the pulse waveform. Peripheral and central parameters were measured using the applanation tonometry probe.

Pulse pressure waveform and amplitude are obtained with a probe that incorporates a high fidelity strain transducer (Model TCB-500, Millar Instruments). Pulse waves are obtained by placing the pencil-like probe perpendicularly over the point of strongest pulsation of the radial artery. The sensor is used to flatten the arterial wall against a bony surface, tangential pressures are eliminated, and the sensor is exposed to the true intra-arterial pressure. The wrist is held dorsiflexed using a support and the probe is applied with steady pressure until a good, recurring waveform signal appears within the display. A good waveform is defined as one that is consistent, large (at least 3 cm on screen) and in a steady position. Twenty consecutive pressure waveforms are recorded, averaged, and peripheral parameters such as dP/dt, the differential of the pressure wave, are obtained.[43] When 20 waveforms are analysed the PHV is calculated. This is a percentage of mean pulse height (difference between maximum and minimum of each pulse). The PHV parameter gives a numerical value and will increase with beat-to-beat pulse height variations, typically as a result of poor quality signals. Diastolic variability is the averaged variability of the diastolic points (minimums) from the mean diastolic as a percentage of the pulse height. It increases with beat-to-beat variations of the minimums and is a measure of how steadily the tonometer is held during the measurements (if the tonometer is held perfectly steady then the PHV% and diastolic variability is zero). Values greater than 4% will not be recorded, and the software programme expects repeat measurements to be made until they fall within 0–4% variability. With the use of the constant transfer function from ascending aorta to the radial artery the aortic pressure waveform and left ventricular function can be measured. The differential pressure wave (dP/dt) that is measured from the radial artery can be used to measure the amplitude of reflected peripheral waves from the vascular tree. When compared with the central cardiac impulse this gives the augmentation index. Left ventricular properties, such as ejection duration and heart rate, can be derived from the aortic pressure wave. This aortic wave can be subdivided into systolic and diastolic components, and allows ventriculo–vascular interactions at baseline and following stressors to be calculated.

Laser Doppler fluximetry

A variety of methods have been used to assess skin viability and tissue micro-perfusion.[48] The principle of laser Doppler flowmetry utilises the fact that a laser light beam incident on tissue is scattered both in static and moving structures (red cells). Light beams scattered in moving red cells undergo a frequency shift according to the Doppler effect, while beams scattered in static tissue alone remain unshifted. A portion of the backscattered light is brought to impinge on the surface of a photodetector where beat notes produced by mixing of waves scattered in different structures are formed. When assessing skin blood flow, laser Doppler flowmetry is found to be more specific and sensitive to changes in blood flow than xenon-washout techniques. This concept has been previously used to predict patency of skin flaps,[49] to visualise the nature of rhythmical variations in healthy human skin,[50] to assess skeletal muscle blood flow,[51] and to assess renal[52] and testicular blood flow.[53] It has also recently been documented that type 1 diabetics have impaired pressure-induced vasodilatation, assessed by laser Doppler flowmeter.[54] The venoarteriolar response (postural vasoconstriction) assessed by laser Doppler flowmetry has also been found to be both reliable and reproducible.[55,56]

Laser Doppler fluximetry is a well-established technique employed in the measurement of the microcirculation following various stimuli, including acute hyperglycaemia and cigarette smoke.[57-60] A laser signal is emitted from a probe. The depth of penetration is determined by the wavelength of emitted light, and the shape is determined by the probe configuration. Therefore, this system measures red blood cell movement in a fixed volume of tissue, which is then an indirect measure of red blood cell flow or 'flux'. There is a small zone of injury around the tip of the probe, but the penetration of the signal is greater and therefore is measuring flux in normal tissues. Measurement of red

blood cell motion is recorded continuously in the outer layer of the tissue under study, with little or no influence on physiological blood flow. This output value constitutes the flux of red cells, defined as the number of red cells times their velocity, and is reported as microcirculatory perfusion units. No direct information concerning oxygen, nutrient or waste metabolite exchange in the surrounding tissue is obtained with this technique. The relationship between the flowmeter output signal and the flux of red blood cells is linear. The beam can penetrate unbroken, non-pigmented tissue to a depth of 1–2 mm. In this study we chose to use one endothelial-dependent and one endothelial-independent stimulus. A postural change from lying to sitting/standing causes a precapillary arteriolar vasoconstriction known as the venoarteriolar reflex, which is thought to protect capillaries by preventing rises in capillary hydrostatic pressure and ultimately transudation and tissue oedema.[61]

Laser Doppler fluximetry results in arbitrary values of flux units. As such there are no absolute measurements of blood flow, and comparisons between baseline and following a stimulus must be made while the Doppler probe is positioned against the skin at the same sitting under the same environmental and study conditions. For this reason it is very difficult to compare baseline flow among groups of subjects, and results are generally given as percent change from an arbitrary baseline.

Serum samples

Haemoglobin, packed cell volume, inflammatory indicators (white cell count, erythrocyte sedimentation rate and C-reactive protein), urea and electrolytes, liver function tests, cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, glucose, glycosylated haemoglobin (HA-8140, Menarini) and frustosamine were assessed at the various time points in both study groups.

Statistical analysis

Statistical analysis was performed with SPSS version 12.0 statistics software. Descriptive statistics as mean ± SEM. ANOVA, with post hoc Tukey-Kramer multiple comparisons testing. The $p<0.05$ level was set as significant. All patients were entered in the study on an intention-to-treat basis and no subjects dropped out or were removed from the study.

Results

Demographics, blood indices and glycaemic control (Table 1)

There were no statistical differences between controls and diabetics in age or BMI. 24-h urinary albumin in diabetics was within the normal reference range (Cobasmiras, Roche).

There were no statistical differences in haemoglobin, inflammatory indicators (white cell count, erythrocyte sedimentation rate and C-reactive protein), urea and electrolytes, liver function tests, cholesterol, low-density lipoprotein, high-density lipoprotein or triglycerides. Packed cell volume was statistically lower in diabetics (0.42 (0.01)) when compared with controls (0.45, $p=0.048$); this was unaltered with treatment. Serum glucose measurements were not significantly elevated in patients with diabetes at the various time points. Glycosylated haemoglobin (HA-8140, Menarini) was statistically higher in diabetics (7.8 (0.9)) compared with controls (4.3, $p=0.010$), This was unaltered throughout the study period. There was a statistical difference in fructosamine levels between controls (236) and diabetics (409) and throughout the study period ($p<0.050$) (see Table 1).

Applanation tonometry: myocardial workload parameters (Table 2)

End Systolic / Mean systolic / Mean diastolic blood pressures There were no statistical differences between controls and patients (baseline, placebo or taurine treated).

Augmentation index Diabetic patients at baseline (2.3 (4.8)) had a statistically higher augmentation index when compared with controls (-10.9 (1.9), $p=0.020$). This was returned to control levels with 2 weeks taurine supplementation (-15.3 (3.5), $p=0.001$) (see Figure 2).

Applanation tonometry: myocardial perfusion parameters (Table 2)

Heart rate Diabetic patients at baseline (69 (2.5) beats/min) had a statistically higher heart rate when compared with controls (58 (3.6) beats/min, $p=0.010$). This was unaltered by taurine or placebo supplementation.

Ejection duration Diabetic patients had a statistically lower ejection duration (298 (7) ms) when compared with controls (324 (9), $p=0.042$). This was unaltered by taurine or placebo supplementation.

Buckberg Index (SEVR) Diabetic patients at baseline (171 (5)) had a statistically lower SEVR when compared with controls (208 (15), $p=0.041$), this was unaffected by either placebo or taurine supplementation.

Brachial artery reactivity (Table 2)

Baseline vessel diameter There were no statistical differences in brachial artery diameter between controls and diabetics and throughout the study period.

Table 1. Demographics, blood indices and glycaemic control.

	Control	DM-Baseline	DM-Taurine	DM-Placebo	*p* value
Age (Years)	29 (1.0)	28 (2.0)	28 (2.0)	28 (2.0)	NS
BMI (kg^2/m)	27.9 (1.2)	22.7 (0.9)	–	–	NS
Haemoglobin (g/dL)	15.5 (0.4)	14.9 (0.3)	14.9 (0.2)	14.7 (0.3)	NS
Haematocrit (PCV)	0.45 (0.009)	0.42 (0.01) $	0.41 (0.006)	0.41 (0.01)	<0.05
White cell count ($X10^9/L$)	5.8 (0.3)	5.8 (0.7)	6.0 (0.7)	5.3 (0.6)	NS
Erythrocyte sedimentation rate (mm/h)	3.9 (0.7)	4.8 (0.7)	3.2 (0.5)	4.2 (1.1)	NS
Total Cholesterol (mmol/L)	4.3 (0.2)	4.7 (0.5)	4.6 (0.4)	4.8 (0.5)	NS
Triglycerides (mmol/L)	1.14 (0.2)	1.2 (0.3)	1.2 (0.2)	1.6 (0.4)	NS
HDL cholesterol (mmol/L)	1.3 (0.06)	1.4 (0.2)	1.4 (0.1)	1.2 (0.1)	NS
LDL cholesterol (mmol/L)	2.5 (0.1)	2.7 (0.4)	2.7 (0.4)	2.9 (0.4)	NS
Serum von Willebrand factor (% control)	71 (4)	110 (10) $	111 (14)	93 (8)	<0.05
Serum glucose (mmol/L)	4.8 (0.2)	9 (2.8)	11 (3.8)	9 (3.4)	NS
Haemoglobin A_{1C}	4.3 (0.3)	7.8 (0.9) $	7.9 (0.9)	7.9 (1.0)	<0.05
Fructosamine	236 (17.5)	409 (70.6) $	422 (55.8)	401 (52.4)	<0.05

Key: DM = diabetes mellitus; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; $ - DM *vs.* Control $p<0.05$

Table 2. Subjects haemodynamic parameters assessed by applanation tonometry, brachial artery ultrasound and laser Doppler fluximetry.

	Control	DM-Baseline	DM-Taurine	DM-Placebo	P value
Myocardial Workload					
End systolic BP (mmHg)	93 (2)	93 (3)	91 (4)	94 (4)	NS
Mean systolic BP (mmHg)	99 (2)	97 (3)	98 (2)	98 (3)	NS
Mean diastolic BP (mmHg)	86 (8)	86 (3)	86 (2)	86 (3)	NS
Augmentation index	–10.9 (1.9)	2.3 (4.8) $	–15.3 (3.5)	0.3 (6.6)	0.001
Myocardial Perfusion Parameters					
Heart Rate (beats/min)	58 (3.6)	69 (2.5) £	71 (4.0)	69 (1.6)	<0.05
Ejection Duration (msec)	324 (9)	298 (7) £	289 (8)	293 (6)	<0.05
Buckberg index (SEVR)	208 (15)	171 (5) £	171 (10)	173 (8)	<0.05
Brachial Artery Reactivity					
Baseline vessel diameter	4.7 (0.2)	4.4 (0.1)	4.6 (0.04)	4.7 (0.3)	NS
Flow-mediated dilatation (%)	9.8 (1.1)	4.0 (0.6) $	9.0 (1.0)	4.3 (0.5)	0.004
Dilatation to GTN (%)	16.9 (1.9)	13.9 (2.1)	15.8 (1.4)	12.7 (1.4)	NS
Laser Doppler Fluximetry					
% Constriction	37 (4.3)	30 (9.3)	30 (12.5)	26 (5.1)	NS
% Dilatation	2113 (615)	794 (299) £	749 (170)	803 (198)	<0.05

Key: DM = diabetes mellitus; BP = blood pressure; SEVR = sub-endocardial viability ratio; GTN = glyceryl trinitrate; $ - DM-Baseline *vs.* Control & DM-Taurine $p<0.05$. £ - DM-Baseline *vs.* Control $p<0.05$.

Endothelial-dependent dilatation (Figure 3) Diabetics had a statistically lower FMD (4.0 (0.6)) when compared with controls (9.8 (1.1), $p=0.001$). This was returned to control levels with 2 weeks taurine supplementation (9.0 (1.0), $p=0.004$).

Endothelial-independent dilatation (smooth muscle dilatation) There were no statistical differences between any of the groups.

Laser Doppler fluximetry (Table 2)

Percentage constriction to leg dependency There was no significant difference between controls and diabetes groups (at baseline, taurine or placebo treated).

Percentage dilatation to heat Diabetics had a statistically lower percentage dilatation (794 (299)) when compared with controls (2113 (615), $p=0.047$), this was unaltered by treatment with taurine or placebo.

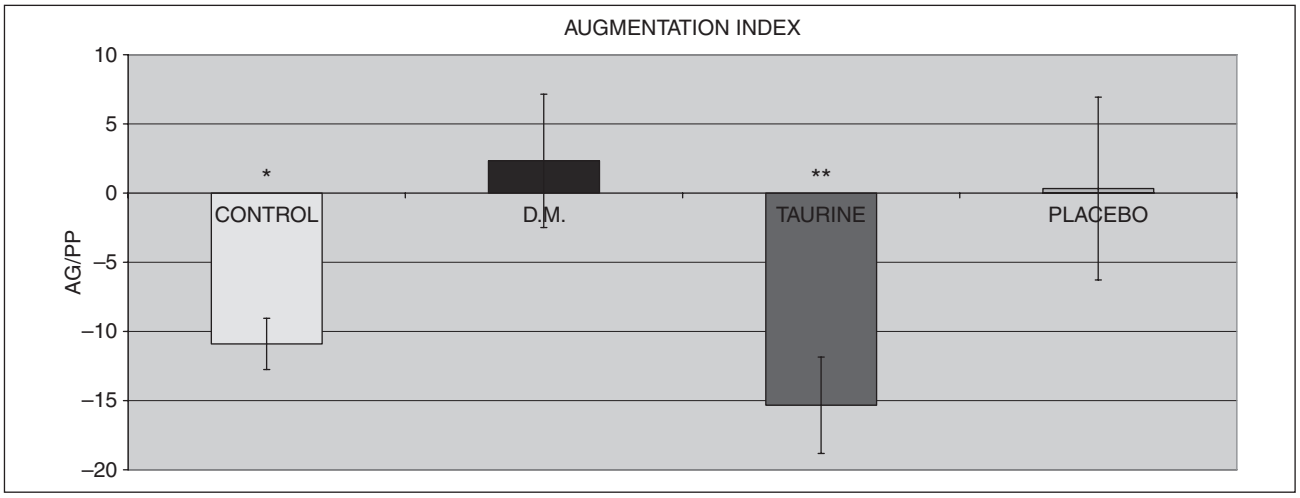

Figure 2. This graph demonstrates the Augmentation index (AI) in controls, diabetics at baseline (DM) and diabetics following supplementation with taurine and placebo for 2 weeks. Diabetics have a statistically higher AI compared with controls (* p=0.020). This is returned to control levels with 2 weeks taurine supplementation (** p=0.001).

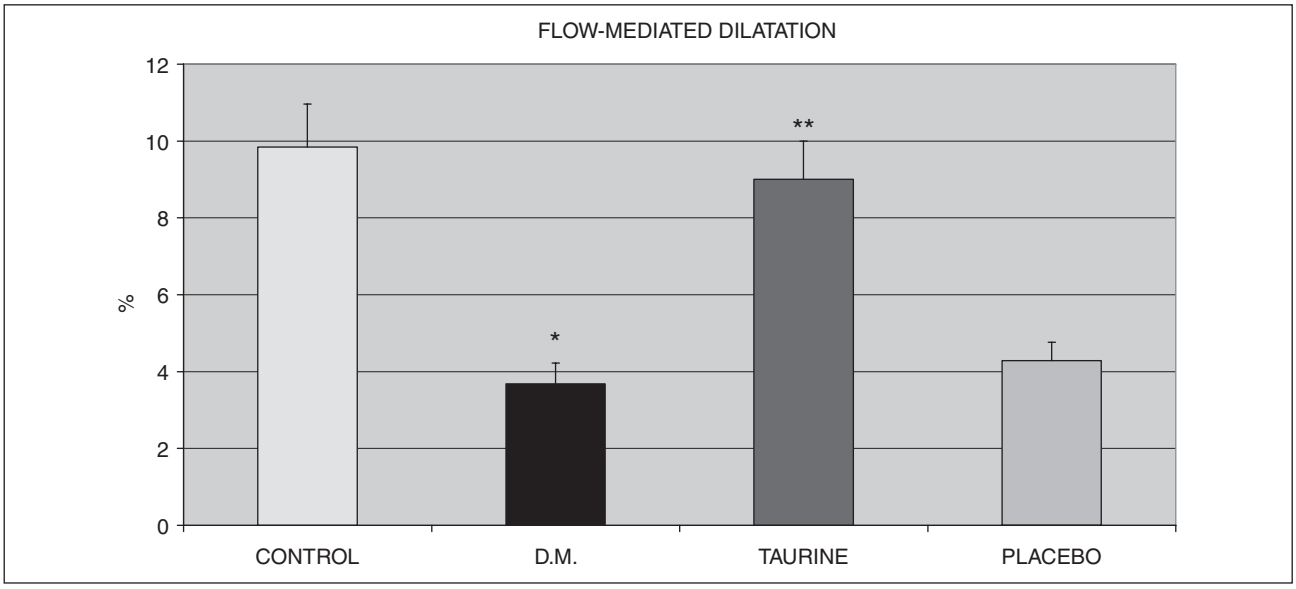

Figure 3. This graph demonstrates the flow-mediated dilatation (FMD) in controls, diabetics at baseline (DM) and diabetics following supplementation with taurine and Placebo for 2 weeks. Diabetics have a statistically lower FMD (* p=0.001) compared with controls. This returned to control levels with 2 weeks taurine supplementation (** p=0.004).

Discussion

This study confirms a multitude of detectable abnormalities in type 1 diabetics, all of which showed excellent glycaemic control. Also, we have for the first time demonstrated that 2 weeks taurine supplementation in young, normoalbuminuraemic, asymptomatic, type 1 diabetics reversed the augmentation index, a marker of arterial stiffness, and restored conduit vessel dysfunction, reflected in improvements in FMD.

Interestingly, in our study population of diabetics there were no statistical differences in glucose levels between controls and diabetics at the various time points. This is a reflection of the diabetic population's tight glycaemic control. Also, short-term glycaemic control, reflected in fructosamine levels, was unaltered in the diabetics across the various time points.

The incidence of many manifestations of coronary artery disease are increased in patients with type 1 diabetes.[62] Indeed, early markers of cardiovascular disease may be present in the absence of clinically detectable disease in diabetes, as reflected in this study in increased arterial stiffness and abnormal conduit vessel function, reflected in decreased FMD.

As with asymptomatic smokers,[63] our patient population of diabetics had a multitude of detectable, pre-clinical abnormalities. Augmentation index, assessed by non-invasive applanation tonometry, was statistically higher when compared with controls, even in the absence of any abnormal myocardial pressures parameters. Type 1 diabetics are reported to have stiffer large arteries in many,[64-66] although not all, studies.[67] Insulin therapy was found to decrease arterial stiffness in uncomplicated type 1 diabetes mellitus.[11] Aortic pulse wave velocity is a recognised independent predictor of mortality in both diabetics and glucose-tolerance-tested population samples. This is strongly correlated with a previous validated estimate of arterial stiffness.[47] Although we found no differences in central pressure parameters in the diabetic population assessed, coexistent raised arterial blood pressure in diabetes is associated with increased cardiovascular morbidity and mortality.[12] Our blood pressure findings are in contrast to previous reports of significant alterations in central pressure parameters in normoalbuminuraemic, type 1 diabetics.[4] This is possibly a reflection of our study population.

Diabetics assessed had multiple myocardial perfusion parameter abnormalities, which were unaltered by taurine. Both ejection duration and the SEVR were statistically lower in diabetics compared with controls. A decreased SEVR is a direct reflection of increased propensity to myocardial ischaemia, and failure to reverse this suggests that pulse rate is the dominant factor in the determination of the Buckberg index.

With regards to conduit vessel function, the diabetic population assessed had a statistically lower FMD when compared with controls. This is in keeping with previously published data.[5,7,9,14] Two weeks taurine supplementation reversed diabetic conduit vessel abnormalities to control values, as assessed by endothelial-dependent dilatation. This most likely resulted from improvements in bioavailability of nitric oxide due to increases in endothelial nitric oxide synthase.[68] Endothelial-independent dilatation, assessed by administration of sublingual GTN, was similar in all groups, thus confirming an endothelial-dependent abnormality as assessed by brachial artery reactivity.

Microcirculatory baseline flow was not statistically different in the diabetics compared with controls. Baseline flow was increased with taurine supplementation, but this was not statistically significant. With regards to the microcirculatory responses, there were no differences in percentage constriction between the groups, but diabetics had a statistically lower percentage dilatation response to heat. This was unaltered by taurine supplementation, possibly reflective of irreversible microcirculatory structural changes in our diabetic population. However, others have questioned both the reproducibility and reliability of the assessment of the skin microcirculatory bed, particularly in diabetics.

Our group, and others, have previously documented improvements in type 1 diabetic conduit vessel function with HMG CoA reductase inhibitors.[4,14] Lifelong incidence of adverse side effects from statin use is, as yet, unpublished. Also, the risk of rhabdomyolysis and other adverse effects with statin use can be exacerbated by several factors, including diabetes.[18]

Taurine, a semi-essential amino acid, therapeutic levels of which can be obtained by dietary manipulation, was found previously to have a hypoglycaemic effect in patients with diabetes mellitus.[20] Several papers have reported that taurine potentiates the effect of insulin,[21] and possibly the insulin receptor.[22] There have been several clinical trials on the assessment of taurine in type 1 diabetics.[23] One study demonstrated that both plasma and platelet taurine levels are reduced in these patients.[24] Oral supplementation returned them to above control levels.[24,25]

The pre-clinical, therapeutic potential of taurine in this 'at-risk' population of normoalbuminuraemic type 1 diabetics is clearly evident. The fact that therapeutic plasma concentrations of the amino acid can be achieved with dietary supplementation supports this strategy in the possible prevention of progression of type 1 normoalbuminuraemic diabetics to clinically overt vascular disease. Studies to evaluate the role of taurine in hyperglycaemic patients, type-2 diabetics and diabetics with microalbuminuria are essential, and assessment of taurine supplementation in these populations is mandatory, particularly in the setting of established cardiovascular disease.

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