Introduction

Obesity and diabetes mellitus type 2 (T2DM) as well as other chronic diseases have been shown to be associated with inflammation and oxidative stress processes [1-3]. Whether the level of these inflammatory and oxidative stress markers differs in obesity and how they interact has not been investigated. Overweight and/or obesity is now estimated to be over 30% of the global population, with approximately 12% being diagnosed with type 2 diabetes mellitus (T2DM) [4,5]. Obesity and diabetes are linked, with the strong association between these diseases resulting in the creation of the term obesity-dependent diabetes or "diabesity" [6,7]. Diabesity is associated with cardiovascular disease (CVD), dyslipidaemia, hyperuricaemia, respiratory disease, osteoarthritis and depression [8]. Two possible pathophysiological mechanisms involved in obesity and T2DM may be associated with diabesity. These two mechanisms are oxidative stress and inflammatory processes. Chronic inflammation as a result of several pro-inflammatory markers such as cytokines and chemokines have been shown to precede weight gain and obesity [9]. Similar observations are seen with a number of oxidative stress markers in obesity [10,11]. The link between inflammatory and oxidative stress markers observed in obesity is also a contributory factor in the development of T2DM and CVD [8,12].

The inflammatory process in obesity includes the activation of macrophages to produce pro-inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-6 (IL-6) [13,15]. These pro-inflammatory cytokines lead to increased levels of C-reactive protein (CRP) with a demonstrable decrease in the anti-inflammatory interleukin-10 (IL-10), IL-1β, IL-6, CRP and IL-10 are linked to abnormal fat and glucose metabolism, which provides further evidence of a link between obesity and diabetes by increasing insulin resistance [8,16].

During the hyperglycaemic state, cytokine production is also accompanied by increased levels of monocyte chemoattractant protein-1 (MCP-1) and decreased levels of insulin-like growth factor-1 (IGF-1) [17,21]. MCP-1 has chemotactic effects, and attracts immune cells such as leukocytes and macrophages to the inflamed sites. It has been shown that an increase in plasma MCP-1 level may cause a macrophage infiltration into adipose tissue and...
Diabetes has been suggested to be a combination of T2DM and obesity with the link being inflammation and oxidative stress [13]. Increased levels of 8-iso-PGF$_2\alpha$ accompanied by an increase in urinary 8-OHdG levels correlating to body mass index (BMI) have been reported in diabetes [11,37]. Several inflammatory markers have also been suggested [19]. The role of inflammatory markers and oxidative stress and how these interact in diabesity has not been extensively investigated when compared to T2DM and obesity and is therefore explored in this study.

**Methods**

The study protocol was reviewed and approved by the Ethics in Human Research Committee of Charles Sturt University (CSU). A total of 270 participants (female: male, 163:107) were selected within a rural diabetes screening clinic at CSU (DiabHealth) for analysis of blood and urine samples. All measurements carried out by clinical staff were in accordance with the relevant legislation, professional standards of practice and policy directives. General biochemistry, including lipid studies, HbA1c, CRP and D-dimer were conducted by the local pathology provider a National Accredited Testing Authority (NATA) laboratory. Enzyme linked immunosorbent assays (ELISA) and GSH were carried out using commercially available kits.

Participants were excluded by age (< 40 years), CVD or kidney disease. As a part of the screening process body mass index (BMI), gender, lipid profile including triglycerides (TG), total cholesterol (TC), high density lipoproteins (HDL)-cholesterol, low density lipoproteins (LDL)-cholesterol and TC/HDL ratio were determined for all participants.

Diabetic participants were selected on the basis of having been diagnosed with an oral glucose tolerance test (OGTT) and/or being prescribed antihyperglycaemic medication. Control participants were included in the study if they had no background of diabetes, cardiovascular, renal or respiratory disease. Participants were comparable for age, gender, smoking and alcohol consumption, diet and physical activity and divided into 4 groups: a control group (FBG <5.6mmol/L and BMI <30.0), a diabetic group (FBG ≥7mmol/L and BMI <30.0), an obese group (FBG <5.6mmol/L and BMI ≥30.0) and an obese diabetic group (FBG ≥7mmol/L and BMI ≥30.0). Fasting blood glucose level (FBG) for the two groups were defined according to the criteria of the American Diabetes Association 2004 [38].

**Sample collection**

Venous blood was collected into EDTA, serum-separating (SST) and sodium-citrate-(SC) tubes. Blood tubes were immediately centrifuged in a Universal 32R (Hettich Zentrifugen, Germany) for 15 min at 800 g. Plasma and serum for inflammatory, coagulation and oxidative stress biomarkers were stored at -80°C until analysis was performed. For measurement of GSH and GSSG, erythrocyte lysates were prepared by washing cells in normal saline followed by the addition of 4 × volume of ice-cold 5% metaphosphoric acid. Post centrifugation lysate was stored at -80°C until analysis.

Midstream urine specimens were collected for the determination of 8-isoprostaglandin F$_2\alpha$ and 8-OHdG. Additional urine aliquots for creatinine and plasma and serum from the blood EDTA, SST and
SC-tubes were referred to the local accredited Dorovitch Pathology Laboratory for lipids, glucose, Hba1c, CRP and D-Dimer levels.

**Anthropometric variables**

Weight was measured using standardized beam weight scales without footwear and with only light clothes. Height was measured with the subjects barefoot and standing with the feet together. Waist circumference was measured in centimeters. BMI, defined as weight in kilogram per height in meters squared and is independent of gender and age was calculated for each client. Overweight clients were classified as a BMI between 25.0-29.9 kg/m² and obese when BMI was equal or greater than 30.0 kg/m² [39]. Blood pressure (BP) was recorded, after patients were rested in a supine position for 5 minutes, using a stethoscope and BP cuff measured at the brachial artery.

A screening fasting blood glucose levels (FBG) was determined on all patients using the Accu-Chek® (Roche Australia Pty Ltd).

**Measurement of oxidative stress and DNA damage**

Urinary 8-isoprostaglandin F$_{2\alpha}$ (8-isopGF$_{2\alpha}$) was determined using OxiSelect™ 8-isoprostaglandin F$_{2\alpha}$ ELISA Kits (Cell BioLabs, INC). The assay incorporates a competitive binding ELISA strategy, allowing the 8-isopGF$_{2\alpha}$ contained in samples and standards to compete with 8-isopGF$_{2\alpha}$ - HRP conjugate for binding to an anti-8-isopGF$_{2\alpha}$ antibody fixed to a goat anti-rabbit antibody pre-coated microplate.

Erythrocyte reduced glutathione (GSH) and oxidized glutathione (GSSG) were determined using the Cayman® Total Glutathione (GSSG/GSH) Assay Kit. Total glutathione was measured by subtracting after the addition of NADPH. GSSG was measured by subtraction with the subjects barefoot and standing with only light clothes. Height was measured using a stethoscope and BP cuff measured at the brachial artery.

**Inflammation biomarkers**

Plasma IL-6, IL-1β, IL-10, MCP-1 and IGF-1 were determined using Human IL-6 ELISA Kit provided by Elisakit.com, Melbourne, Australia.

**Coagulation and fibrinolysis**

Plasma C5a was determined using Human C5a Platinum ELISA (eBioscience, Affymetrix, North America).

All ELISA measurements conducted on the inflammatory, oxidative stress and coagulation biomarkers were carried out with a Thermo Scientific Multiskan FC (Fisher, China). Data analysis for the ELISA analysis utilised a 4-parameter logistic curve fit.

**Statistical analysis**

Descriptive data was expressed as mean ± standard deviation (X ± SD). Statistical analysis was performed with SPSS (Version 20, IBM Co). To determine if there were significant differences in biomarker levels between the control, the diabetic, the obese and the obese diabetic group, an analysis of variance (ANOVA) was used. To correct for age and gender, an analysis of covariance (ANCOVA) was used. A p-value 0.05 was considered as significant.

**Results**

Anthropometric, clinical and biochemical data for the 270 patients who participated in the study and for whom blood and urine samples were available are shown in Table 1. Comorbidities and medication history were noted and documented.

BMI – Body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, TC – Total cholesterol, HDL – high density lipoprotein, LDL – low density lipoprotein.

Significant differences were found for anthropometric data including age, waist circumference and BMI, which increased from control to T2DM, obese and diabesity status. Waist circumference for females was lower than for men in all groups, with significant differences for both genders between all groups other than the obese and diabesity group in the male cohort. There were significant differences in systolic blood pressure (SBP) between the control, T2DM and diabesity groups. General biochemistry profiles including.

**Table 1: Anthropometric and general biochemistry data.**

| Medication (n,%) | Control | T2DM | Obese | Diabesity |
|-----------------|---------|------|-------|-----------|
| NSAID | 52 (39.4 %) | 26 (45.5%) | 12 (32.4%) | 28 (63.6 %) |
| AntiHT | 40 (30.3%) | 26 (73.7%) | 20 (10.8%) | 32 (72.7%) |
| Statins | 26 (18.7%) | 42 (73.7%) | 4 (10.8%) | 32 (72.7%) |
| Dmeds | 0 | 45 (78.9%) | 0 | 36 (81.8%) |

**Significant differences**

a-Significant result between control and T2DM (p<0.05)
b-Significant result between control and obese (p<0.05)
c-Significant result between control and diabesity (p<0.05)
d-Significant result between T2DM and obese (p<0.05)
e-Significant result between T2DM and diabesity (p<0.05)
f-Significant result between obese and diabesity (p<0.05)

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein.
screening fasting glucose and HbA1c were elevated in T2DM and diabesity but were low in obese with some significant differences between groups. Lipid profiles also showed significant differences between the groups (Table 1).

Coagulation and fibrinolysis investigated with C5a and D-dimer showed no significant differences between groups in our study. However C5a results trended upwards in the diabetic group compared to control and decreased again in the obese and diabesity groups.

Figure 1 indicates a significant difference for GSH between the T2DM (1456.6 µM/mL ± 737.5, p<0.03) and obese groups (1890.7 µM/mL ± 823.3, p<0.003). However GSSG levels did not show significant differences between any of the other groups. 8-OHdG increased significantly in the obese group (185.5ng/mL ± 162.4, p<0.03) compared to the control group (146.8ng/mL ± 127.5) with a further nonsignificant increase in the diabesity group (204.6ng/mL ± 286.8). The obesity group (185.5ng/mL ± 162.4) was significantly increased to the T2DM group (119.2ng/mL ± 92.9, p<0.03). The T2DM group results (119.2ng/mL ± 92.9) were less than the control group but were not significant (Figure 1). A significant increase was also found in 8-iso-PGF$_{2α}$ in the diabesity group (2.3 ± 15.0 ng/mL) compared to the control group (1.0 ± 1.9 ng/mL, p<0.03) and the T2DM group (1.1±2.5ng/mL, p<0.05). The diabesity group (2.3 ± 15.0 ng/mL) was significantly increased to the obese group (1.1ng/mL ± 1.8, p<0.03). A slight but not significant increase in the T2DM and obese groups was also found for 8-iso-PGF$_{2α}$ (Figure 1).

Results for CRP levels for all groups compared to the control (1.0mg/L ± 1.50) were significantly higher for the obese group (4.0mg/L ± 5.80, p<0.001) and the diabesity group (2.0mg/L ± 4.0, p<0.05). There was also a significant increase between the obese group (4.0mg/L ± 5.80, p<0.05) and the T2DM group (1.0mg/L ± 2.20) (Figure 2). CRP levels decreased between obese group and diabesity, however results were not significant. IL-6 results showed no significant difference between any groups, however the T2DM group did demonstrate an increase above the other groups including the control group. IL-1β levels were significant between the control (3.70pg/mL ± 10.10) and obese groups (2.20pg/mL ± 2.70, p<0.03), the T2DM (3.10pg/mL ± 7.0) and obesity groups (2.20pg/mL ± 2.70, p<0.05) and the obesity and diabesity group (7.10pg/mL ± 12.50, p<0.05). IL-10 decreased slightly but not significantly from the control group to the T2DM group and obesity group, but did increase significantly between the obese group (16.20pg/mL ± 13.20) and diabesity group (23.60pg/mL ± 82.30, p<0.03). No significant results were obtained for MCP-1 between any groups. IGF-1 revealed a significant decrease in the control (302.8pg/mL ± 547.2) and T2DM (225.1pg/mL ± 417.0, p<0.05) and the diabesity group (144.6pg/mL ± 285.7, p<0.03) (Figure 2). There was a trending down of IGF-1 in all groups observed.

To further our investigations into inflammatory marker interactions we also performed comparisons with inflammatory marker ratios: IL-6/IL-10, IL-1β/IL-10, (MCP-1/IGF-1)*IL-6 and (MCP-1/IGF-1)*IL-1β ratios. The IL-6/IL-10 ratio was significantly
higher in the obesity group (0.71 ± 1.94) versus the control group (0.17 ± 0.35, p<0.03), the level of significance between the obesity group and the diabesity group (0.47 ± 0.66) was p<0.06. IL-1β/IL-10 and (MCP-1/IGF-1) IL-1β results were not significant. However the (MCP-1/IGF-1) IL-6 results showed an increasing but not significant trend.

Discussion

Diabesity is related to several comorbidities and chronic disease states, which may all have a pathophysiological basis in oxidative stress and inflammation. Previous studies have related obesity dependent diabetes to an increase in inflammation, and have shown that biomarkers of inflammation interact with each other. In the current study we have shown that the ratio of IL-6, MCP-1 and IGF-1 was the lowest in the control group and increased with obesity, diabetes and diabesity. During the inflammatory process as part of chronic disease pathophysiology an increase of proinflammatory biomarkers (IL-6, IL-1β) coupled with a decrease in anti-inflammatory biomarkers (IL-10) has been demonstrated [13-16]. Other studies have shown that IL-6 and IL-1β also increased MCP-1 levels by inducing MCP-1 mRNA expression [40-43]. These two proinflammatory biomarkers also inhibit IGFBP-2 and IGFBP-4 secretion resulting in a decrease in IGF-1 levels [44-47]. A negative feedback loop between IGF-1 and MCP-1 then also decreases MCP-1 [48]. Our study demonstrated that the increase in the IL-6/IL-10 ratio between control and obesity was significant but dropped back down in the diabesity group. This drop still remained higher than the control and the T2DM group and suggests a cyclic interaction or negative feedback loop between these inflammatory markers and other biomarkers involved in disease progression. This is further confirmed with CRP being significantly increased in the obese and diabesity groups compared to control. In our study a significant decrease was observed in IGF-1 for the diabesity compared to the control group. The significant changes in the inflammatory markers in this clinical study were found despite...
patients being on several medications such as statins, antidiabetic and antihypertensive medications suggesting their utility in clinical practice as diabesity risk markers.

A similar association was seen for oxidative stress markers. We observed a significant increase in 8-iso-PGF$_2\alpha$ in the diabesity group and between the obesity and T2DM groups. These results are indicative of lipid peroxidation increasing due to oxidative stress occurring in the diabesity state similar to T2DM and obesity and demonstrates the potential for 8-iso-PGF$_2\alpha$ as a marker of oxidative stress in the development of the diabesity state. A significant increase in 8-OHdG levels in the T2DM and obese groups compared to controls was also observed. Oxidative stress is apparent in diabesity and should therefore be subject to further analysis to confirm our findings.

A novel finding was that the IL-6/IL-10 ratio was significantly different between the control group and the obesity group with the difference between the obesity and diabesity group were approaching significance (p<0.06), indicating that further research is required with increased cohort numbers to assess the role of IL-6/IL-10 in diabesity. The (MCP-1/IGF-1)*IL-6 while not significant did trend upwards throughout the four groups, whereas the (MCP-1/IGF-1)*IL-1$\beta$ ratio appeared to trend down with the obese group and upwards with the diabesity group. We have previously observed significant differences in IL-6/IL-10, as a measure of the pro/anti-inflammatory response in endurance training and high intensity interval training when compared to a control group [49]. Our own work on mild cognitive decline also suggests that the interaction between IL-6 and IL-10 measured as a ratio is part of the pathophysiological process [50]. Analysis of inflammatory ratios may therefore provide additional information on the pathophysiology of diabesity.

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