



Impaired Fasting Glucose & 8-Iso-Prostaglandin F_{2α} in Diabetes Disease Progression

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Authors' contributions

This work was carried out in collaboration between all authors. Authors HFJ and HAA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author DAJ managed the analyses of the study. Author HFJ managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: The objective of the present study was to evaluate the changes of 8-isoprostaglandin F_{2α} and other markers of oxidative stress with impaired fasting glucose when compared to non-diabetic control participants.

Methodology: This is a cross-sectional study, conducted at Charles Sturt University, Albury, NSW, Australia and included 428 participants (female: male, 247:181) participants attending the Diabetes Complications Clinic in the School of Community Health for the period between January 2011 to October 2012.

Results: Urinary 8-isoprostaglandin F_{2α} was significantly greater in the impaired fasting glucose group (1.4±1.3ng/ml) compared to control group (0.68±0.5ng/ml, $P = .05$). The increase in urinary 8-isoprostaglandin F_{2α} was associated with a significant elevation in serum total cholesterol (4.7±1.1mol/L, $P = .04$) and a significant reduction in high density lipoprotein cholesterol (1.4±0.4mmol/L, $P = .02$) in the impaired fasting glucose group compared to the control group. A significant negative correlation was noted between urinary 8-isoprostaglandin F_{2α} and high-density lipoprotein cholesterol among all the participants included in this study ($P = .05$).

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Conclusions: The current study proves the importance of measuring markers of oxidative stress, expressed by urinary 8-isoprostaglandin $F_{2\alpha}$ and serum lipids in managing cases of impaired fasting glucose and suggests a useful biomarker for assessing disease progression and/or remission, especially in the prediabetic state.

Keywords: Oxidative stress; impaired fasting glucose; 8-isoprostaglandin $F_{2\alpha}$; serum lipids.

1. INTRODUCTION

Patients with diabetes mellitus type 2 (DMT2) have an impaired redox state, with impaired antioxidant activity primarily associated with the glutathione-glutathione disulfide (GSH: GSSG) redox, thioredoxin-1 and plasma cysteine/cysteine reactions [1-3] as hyperglycemia causes cellular oxidative stress, which through generating free radicals, leads to diabetes complications, some of which may already manifest in the impaired fasting glucose (IFG) stage [4,5]. Cardiovascular disease, as a complication of diabetes progression, develops as a result of transient or chronic hyperglycemia due to polyol pathway flux, formation of advanced glycation end products and over activity of the hexosamine pathway [6-8]. These pathophysiological changes are in turn linked with lipid peroxidation, oxidative stress, and inflammation seen in IFG and diabetes [9]. Lipid peroxidation is most often measured using malondialdehyde (MDA) and 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-PGF $_{2\alpha}$) [10-12]. Oxidative stress can be determined by GSH and 8-hydroxy-2-deoxyguanosine (8-OHdG) assays [13-15]. GSH is a global antioxidant primarily located in erythrocytes, while 8-OHdG is correlated with endothelial DNA damage caused by oxidative stress.

Increased fasting blood glucose (FBG) and postprandial blood glucose (PBG) levels, glycated hemoglobin (HbA1c), low density lipoprotein-cholesterol (LDL-C) and triglycerides (TG) are associated with oxidative stress progression and diabetes complications. IFG can lead to atherosclerosis through glucose self-oxidation, protein oxidation and lipid peroxidation [16-20]. Progression of atherosclerosis in turn leads to an increase in 8-OHdG, interleukin-6 (IL-6), C-reactive protein (CRP), MDA and 8-iso-PGF $_{2\alpha}$ [12,14,21].

The pathophysiological imbalance between LDL-C, high density lipoprotein-cholesterol (HDL-C), triglycerides and blood glucose levels (BGL) are already present in the IFG state and increases the risk of coronary heart disease and arrhythmia [13,22-25]. Impaired fasting glucose is a preclinical stage of diabetes characterized by intermittent or chronic increases in BGL above 5.5 mmol/L and below 7 mmol/L [26]. Increased levels of BGL and triglycerides have been shown to be associated with increased endothelial dysfunction and oxidative stress [27,28].

Isoprostanes are stable products of arachidonic acid peroxidation due to free radical activity and reliable biomarkers for oxidative stress, which are suitable for measures of lipid peroxidation in place of MDA [29]. Isoprostanes, including 8-iso-PGF $_{2\alpha}$ are stable in biological fluids and easily detectable as well as not being affected by diet and modulated by endogenous antioxidants [30]. Plasma levels of 8-iso-PGF $_{2\alpha}$ have been associated with atherosclerosis and coronary artery disease as well as DMT2 [31-33]. In contrast to cross-sectional studies where 8-iso-PGF $_{2\alpha}$ have been shown to be increased in type 2 diabetes, longitudinal studies have shown an inverse relationship between the level of 8-iso-PGF $_{2\alpha}$ and risk of diabetes independent of traditional risk factors [33,34]. This inverse relationship may occur due to either lower levels of HDL-C or HDL-C losing some of its antioxidant

potential with increased blood glucose levels or hypertriglyceridemia affecting redox balance differently.

Multiple metabolic pathways are therefore associated with oxidative stress and the development of diabetes and its complications. Whether these changes are seen in impaired fasting glucose and the relationship between antioxidant activity cholesterol and isoprostane levels is not clear and this paper aims to elucidate some of this [35].

2. METHODOLOGY

Data for this study was obtained from patients attending the diabetes complications clinic at Charles Sturt University, Albury, NSW, Australia. All participants were recruited via public media announcements. Those with diabetes, cardiovascular or renal disease were excluded from the analysis. Twenty-five participants with IFG were included in this study. IFG was set between 5.5mmol/L to 7mmol/L in accordance with the American Diabetes Association [36]. Thirty-eight subjects were included in the control group. The research was approved by the Human Ethics in Research Committee, Charles Sturt University. Medications used by the participants are listed in (Table 1).

Table 1. Medications used by the participants in this study

	Control (n=38)	IFG (n=25)	P
Aspirin/clopidogrel	9	4	ns
Statins	8	14	.04
Antihypertensives	12	14	.006
Diuretics	3	4	ns

**ns-non significant*

After an overnight fast, whole blood specimens were collected into heparin and EDTA tubes for analysis. Plasma was separated within 1 hour by centrifugation at 1000 x g for 10 min. Plasma from heparin-containing tubes was immediately used for lipid analysis. Plasma from EDTA-containing tubes was kept at -80°C for serum 8-OHdG and GSH analysis. Fresh blood was kept on ice for not more than 1 hour to measure GSH. The level of erythrocyte reduced glutathione (GSH) was determined using the 5, 5'-dithiobis-2-nitrobenzoic acid (DTNB) reaction [37]. 8-isoprostane was determined by a urinary Isoprostane ELISA Kit (Northwest, USA), which uses a competitive ELISA strategy, allowing the 8-isoprostane contained in samples and standards to compete with a 8-isoprostane-horseradish peroxidase conjugate for binding to a specific antibody pre-coated on a microplate. The blue colour development after addition of the horseradish peroxidase substrate is inversely proportional to the amount of 8-isoprostane in the samples and standards and changes to yellow after stopping the reaction with acid. Absorbance is measured at 450 nm. Urine 8-OHdG was measured using an EIA Kit, Cayman Chemical, MI, USA [38]. The test utilizes an anti-mouse IgG-coated plate and a tracer consisting of an 8-OHdG-enzyme conjugate, which detects all three oxidized guanine species; 8-hydroxy-2'-deoxyguanosine from DNA, 8-hydroxyguanosine from RNA and 8-hydroxyguanine from either DNA or RNA. This format has the advantage of providing low variability and increased sensitivity compared with assays that utilize an antigen coated plate and only detect 8-hydroxy-2'-deoxyguanosine. 8-iso-PGF_{2α} was also measured using an EIA Kit, Cayman Chemical, MI, USA.

Fasting plasma total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) were measured by standard techniques. TC and TG were determined

with a commercial enzymatic kit. HDL-C was determined by immunoinhibition assay. Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula [39].

Statistical analysis: The data was analyzed using SPSS (Version 14) and Microsoft Excel (Office 2007, Microsoft). All values were expressed as mean \pm standard deviation (M \pm SD). Statistical analysis was performed using an independent sample t-test. In all tests, $P < .05$ was considered to be statistically significant. Power analysis was performed for a median effect size and high power, providing a sample number of 27 with a p value of 0.05

3. RESULTS

During the screening period of January 2011 to October 2012, 428 participants (female: male, 247:181) attended the diabetes screening clinic. After exclusions, 25 participants were identified with an impaired fasting blood glucose levels (IFG) in the range defined by the American College of Endocrinology [36] and 38 participants had no IFG/diabetes. Table 2 shows the demographics and biomarker results of the study.

The blood glucose level (BGL) was significantly different between the two groups as expected with a near statistically significant rise in HbA1c in the IFG group ($P = .052$). 8-iso-PGF2 α was significantly elevated in the IFG group ($P = .02$) (Fig. 1). Both total cholesterol and HDL-C were significantly lower in the IFG group, while triglycerides and LDL-C showed no difference between the groups (Table 2).

Table 2. Demographics and biomarkers of the study population

Parameters	Control(38)	IFG(25)	P value
Age (yrs)	64 \pm 11	65.4 \pm 9	ns
Male/Female ratio	17/21	11/14	ns
BGL (mmol/L)	4.9 \pm 0.5	6.3 \pm 0.4	.001
HbA1c (%)	5.7 \pm 0.7	6.2 \pm 0.6	ns (.052)
BMI (kg/m ²)	25.7 \pm 4.4	26.4 \pm 5	ns
TC (mmol/L)	5.4 \pm 0.9	4.7 \pm 1.1	.04
Triglycerides (mmol/L)	1.2 \pm 0.6	1.3 \pm 0.7	ns
HDL-C (mmol/L)	1.7 \pm 0.5	1.4 \pm 0.4	.02
LDL-C (mmol/L)	3.1 \pm 0.8	2.6 \pm 0.9	ns
TC/HDL-C	3.3 \pm 0.9	3.5 \pm 1	ns
8-OHdG (ng/ml)	119.3 \pm 81.2	132.6 \pm 108.5	ns
GSH (mg/100ml)	68.4 \pm 16.2	58.9 \pm 21.5	ns
GSSG (mg/100ml)	28.9 \pm 17.9	21.6 \pm 8.9	ns
GSH:GSSG	6.6 \pm 4.4	6.1 \pm 3.2	ns
8-iso-PGF2 α (ng/ml)	0.68 \pm 0.5	1.4 \pm 1.3	.02
AIP	-0.18 \pm 0.3	-0.09 \pm 0.27	ns

*ns-non significant

The atherogenic index of plasma (AIP), which reflects the balance between atherogenic and protective lipoproteins, was in the normal range for both groups suggesting a low risk of CVD. Oxidative stress measured by 8-OHdG was elevated with redox balance (GSH:GSSG) reduced but neither reached significance (Table 2).

Pearson correlation analysis showed a significant negative correlation between 8-iso-PGF_{2α} & HDL-C (Table 3). This correlation wasn't significant with other parameters of this study (Table 3).

Table 3. Pearson correlation between significant markers found in this study

Parameters	HDL (mmol/L)	Isoprostane (ng/ml)	HbA1c (%)
Isoprostane (ng/ml)	-0.4(0.002)*		
HbA1c (%)	-0.27(0.07)	0.2(0.15)	
TC (mmol/L)	0.4(0.001)	-0.4(0.001)	-0.16(0.25)

*Pearson Correlation Coefficient (P value <.05)

No significant difference in 8-iso-PGF_{2α} was observed when statin use was considered in the analysis (Fig. 1).

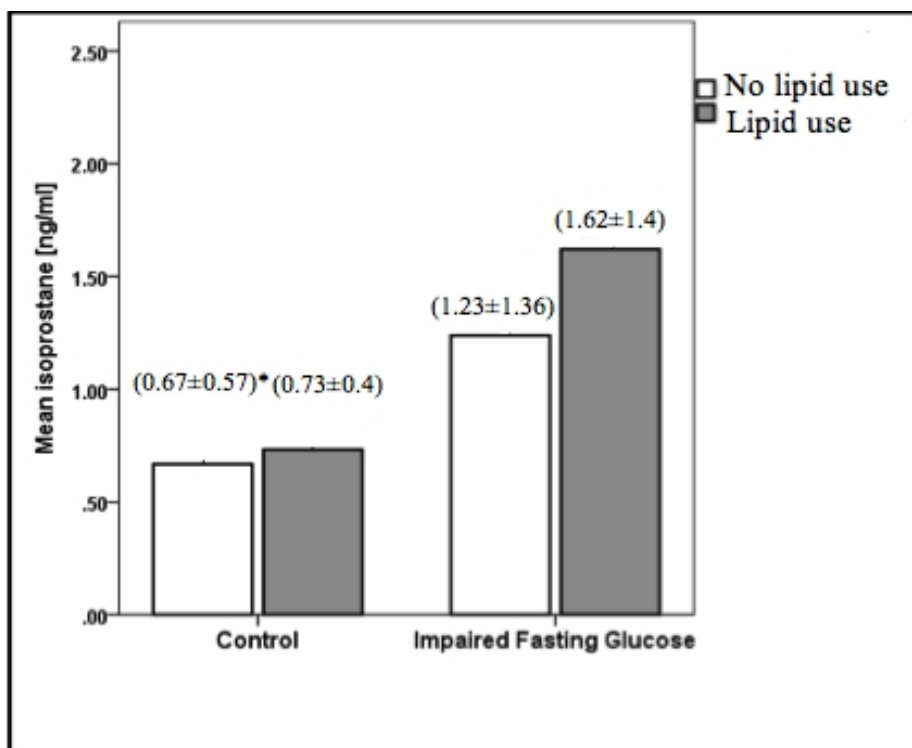


Fig. 1. The mean values of 8-iso-PGF_{2α} in both the control group and the IFG group with and without the use of lipid lowering medication

4. DISCUSSION

Our data demonstrates a significant increase in 8-iso-PGF_{2α} in the IFG group, which means that lipid peroxidation is definitely present during the IFG stage and supports Gopaul, et al.'s findings that 8-iso-PGF_{2α} was increased following an oral glucose tolerance test in individuals with no diabetes but with either IFG or impaired glucose tolerance [40]. These authors suggested that oxidative stress identified by elevated 8-iso-PGF_{2α} levels precedes

glucose intolerance and insulin resistance. However other studies argue for no direct causal link between 8-iso-PGF_{2α} and a decrease in insulin sensitivity [41]. This indicates the presence of other oxidative stress associated pathways and the necessity to identify these to better understand disease progression even into the preclinical domain. Changes in serum lipids in type 2 diabetes have also been demonstrated in the IFG stage and are associated with oxidation of arachidonic acid to 8-iso-PGF_{2α} [42,43,37]. In our current study there was a significant reduction in both total cholesterol and HDL-C, which explains the increased 8-iso-PGF_{2α} as HDL-C carries 8-iso-PGF_{2α} [11]. Of importance is that no significant change in serum lipids in response to the statin use was noted. This may be related to the fact that LDL-C does not play a major role in diabetes disease progression. Furthermore, the type of statin medication used may possess variable effects on lipid peroxidation and oxidative stress and hence variation in the levels of 8-iso-PGF_{2α} [22,44].

The increase in 8-iso-PGF_{2α} shown in the current research is associated with a non-significant decrease in GSH and GSSG with a concomitant increase in 8-OHdG. The decrease in GSH suggests that the intracellular erythrocyte pool is depleting due to its role in the detoxification of aldehydes associated with lipid peroxidation [45] but in our study it has not reached a significant value.

It is worth mentioning here that IFG forms approximately 15% of the patients newly diagnosed with high blood glucose and is confirmed by either impaired fasting glucose or impaired glucose tolerance [46]. IFG can be viewed as a multifactorial disease with increased risk of developing diabetes mellitus and its complications. Therefore the etiology of IFG needs to be carefully determined with reference to the multiple biochemical pathways associated with hyperglycemia and associated oxidative stress and inflammation.

5. CONCLUSION

The current study illustrates that lipid peroxidation, expressed by urinary 8-isoprostaglandin F_{2α} is already present in IFG. In addition, oxidative DNA damage and impaired antioxidants, which may be associated with endothelial dysfunction may be present at this stage as demonstrated by the increased 8-OHdG and decreased GSH levels. These findings provide a useful way of assessing disease progression and/or remission in response to the treatment.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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