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ORIGINAL ARTICLE

Hormone imbalances detected in study participants with pre-diabetes in a Durban-based clinical setting, South Africa

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Abstract

Background Type II diabetes mellitus onset is linked with hormonal imbalances. However, the knowledge about hormonal alterations in pre-diabetes is limited.

Objective The study aimed to examine type II diabetes mellitus-associated hormone levels during the pre-diabetes phase in participants aged 25–45 in a Durban-based clinical setting in South Africa.

Methods Stored plasma samples from a retrospective study collected 364 samples that were divided into pre-diabetes and non-pre-diabetes groups. From the 364, 38 samples from the group of persons without pre-diabetes and 38 from persons with glycated haemoglobin determined pre-diabetes were blindly selected. The hormone concentrations (C-peptide, cortisol, adipokines, thyroids, incretins, and sex steroids) of the study participants were measured using the BIO-RAD Bio-Plex MAGPIX instrument.

Results Hormone imbalances in several hormones were detected in study participants with pre-diabetes. Most of the hormone dysregulation associated with T2DM begins in pre-diabetes but at a moderate level.

Conclusion The findings reveal new possible hormone therapy targets for pre-diabetes and contribute to the growing support for targeting pre-diabetes as a preventative measure for T2DM prevention.

Keywords Pre-diabetes · Intermediate hyperglycaemia · Glycated haemoglobin · Incretins · Adipokines · Sex steroids · Thyroid hormones

Introduction

The African region has the highest proportion (73%) of deaths linked to diabetes in persons aged below 60 years [1, 2]. The prevalence of Type II Diabetes Mellitus (T2DM) continues to rise, especially in developing countries [2, 3]. This adverse metabolic disease is characterised by hyperglycaemia caused by insulin resistance, insufficient insulin production, or both. The elevated blood glucose levels seen in T2DM are linked with hormonal imbalances. Nevertheless, T2DM will often be preceded by pre-diabetes [4, 5]. The pre-diabetic state is defined as an intermediate state of hyperglycemia, whereby the glucose concentration in the blood is higher than usual but below the T2DM threshold [6–9]. Pre-diabetes is considered a viable target for preventative measures to attenuate the rising prevalence of T2DM [10]. However, in hormonal imbalances, pre-diabetes remains underexplored when compared to T2DM.

In T2DM, studies have shown that hormonal differences between the sexes influence the prevalence of diabetes [11]. The imbalance of sex hormones such as progesterone, estradiol and testosterone were linked with the development of T2DM [12–14]. The stress hormone cortisol was reported to alter insulin sensitivity in fat and muscle cells, thus rendering them resistant [15–18]. Incretins such as GLP-1 and GIP are another group of hormones that regulate glucose metabolism by promoting pancreatic beta-cells to secrete the hormone insulin. In T2DM, the incretin hormone levels are dysregulated, resulting in hyperglycaemia [19, 20]. In addition, thyroid and adipokine hormone changes in the blood are associated with the development of T2DM. These investigations into hormonal imbalances in T2DM have assisted immensely in T2DM care and in creating antidiabetic drugs like GLP-1 agonists and Tirzepatide. Whether or not the

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dysregulation of hormones observed in T2DM will reflect in pre-diabetes remains elusive.

Pre-diabetes shares similar metabolic characteristics to T2DM. Yet the relationship between pre-diabetes and hormonal imbalances is not well studied. The outcomes have the potential to reveal specific hormone imbalances in pre-diabetes that can be considered therapeutic targets to improve pre-diabetes care and prevent T2DM onset. Therefore, the objective of the study was to appraise whether or not these hormone imbalances exist in individuals diagnosed with pre-diabetes aged between 25 and 45 in a Durban-based clinical setting.

Methods and Materials

Study design

Ethical approval was obtained from the Ethics Committee of the University of KwaZulu Natal (Study ref: BE266/19). The study was part of a retrospective study. The initial data and sample collection were conducted, from March 2022 to November 2022 at the King Edward Hospital located in an urban area of Durban, South Africa, a developing country. Three hundred and sixty four (364) persons aged 25–45 participated, of which 76 samples were selected in a blind study where only their diabetes status was known. The 76 samples included 38 samples selected from the group without pre-diabetes, and the other 38 were selected from the group with pre-diabetes.

The inclusion and exclusion criteria for the study are described as follows: The included samples had to be from participants of any ethnicity who fell within the age group of 25 – 45 years. The 25–45 age limit was chosen to eliminate the influence of the ageing factor on hormone concentration changes [21]. The American Diabetes Association (ADA) criteria were used to diagnose pre-diabetes by measuring the glycated haemoglobin (HbA1c). The ADA criterion confirms pre-diabetes with an HbA1c value between 5.7–6.4%. Therefore, for eligibility, the patients had to be within the age range of 25–45, have an HbA1c of less than 6.5%. Haemoglobin variants, kidney failure, anaemia, pregnancy, and medications such as opioids are known to affect the reliabilities of HbA1c readings. To circumnavigate these conditions, study participants with hypertension, anaemia, kidney disease, liver disease, a previous history of diabetes and who were pregnant were excluded. Furthermore, the impaired fasting glucose results were also used to validate HbA1c outcomes.

Clinical data collection and biochemical analysis

All participants were asked to fast overnight and arrive in the morning for blood collection. Therefore, the blood samples of all participants were drawn in the morning. In turn, the diurnal variation in any hormonal concentrations was minimised. The fasting blood glucose was measured from study participants who fasted overnight. Before the whole blood was separated, the HbA1c was measured using a clinically validated NGSP and IFCC-certified, laboratory-based Tosoh G8 HPLC Analyzer [22]. The analyser is an ion-exchange HPLC instrument for separating and quantifying HbA1c in whole blood. The whole blood was centrifuged (Eppendorf centrifuge 5403, Germany) to collect plasma that was stored in a -80 °C freezer (Snijders Scientific, Holland). The Luminex MAGPIX System was utilised to measure the hormone concentrations in plasma samples using Multiplex immunoassays. The manufacturer's instructions were followed for each immunoassay kit (MilliPlex, Merck, USA and Procarta Plex, ThermoFisher, USA).

Statistical analysis

A normality test assessed whether or not the data was parametric or non-parametric. Parametric data were presented as Mean ± 95% Confidence Interval (CI) and Median + Interquartile range for non-parametric data or in proportion (percentage) where appropriate. To compare the two groups, the Independent Student's t-test or Mann–Whitney U test was utilised for parametric and non-parametric data to detect the difference between them. Spearman correlation analysis was conducted to determine hormones that are associated with HbA1c. Given that gender is a possible confounder for hormone concentrations, the data was therefore stratified by gender in Table 1.

Results

Various T2DM-linked hormonal imbalances in persons with pre-diabetes compared to persons without were investigated. This was achieved by conducting multiplex analyses containing the hormones of interest. The study outcomes showed that specific hormone concentrations are dysregulated significantly in the Pre-Diabetes (PD) group compared to the Non-Diabetes (ND) group in the pre-diabetes condition.

The characterisation of study participants is recorded in Table 2. The multiplexed assay results for hormone concentrations are recorded in the Fig. 1 layout. The adipokines (adiponectin and adipsin), thyroid (T3 and T4), GIP, C-peptide, sex steroids (testosterone, estradiol and progesterone), and cortisol hormones were elevated in the pre-diabetes (PD) group when compared to the non-prediabetes (NPD) group ($p < 0.05$). In Table 3, the Spearman correlation analysis indicates that c-peptide, cortisol, progesterone, estradiol, T3, T4, and adiponectin are correlated with the HbA1c significantly.

Table 1 Characteristics of persons in the NPD PD groups of participants involved in analysing hormonal changes

	Non-Pre-Diabetes (NPD) 38	*Pre-diabetes (PD) 38*
Age; mean (95% CI)	37,45 (35,47- 39,42)	37,82 (35,77—39,86)
Race		
African	25 (66%)	24 (63%)
White	6 (16%)	2 (5%)
Indian	7 (18%)	10 (26%)
Coloured	0 (0%)	2 (5%)
Gender		
Male	13	18
Female	25	20
IFG, median (IQR), mmol/l	5,7 (0,7)	6,5 (0,5)
HbA1c, mean % (95% CI)	5.3% (5,2–5,4)	6.1% (6,0—6,2)
Insulin, median (IQR) pg/ml	12,232 (11,341—13,123)	12,413 (11,789—13,037)

The data are presented as mean (95% CI) or median (IQR) depending on the normality and proportion

Table 2 Hormones that are correlated with changes in HbA1c

Correlation	HbA1c, Spearman r value	95% CI	*p* value
HbA1c	1	1,000 to 1,000	0,000
Male	-0,141	-0,37—0,07	0,22
C-peptide	0,343	0,02—0,49	0,006 **
Cortisol	0,314	-0,08—0,43	0,018 *
estradiol	0,501	-0,03—0,42	< 0,001 ***
Progesterone	0,626	0,37- 0,70	< 0,001 ***
Testosterone	0,216	-0,09—0,36	0,064
T3	0,384	0,12—0,53	< 0,001 ***
T4	0,355	0,10—0,52	0,002 **
Adiponectin	-0,314	-0,53—-0,12	0,006 **
Adipsin	0,195	0,02—0,45	0,099
GIP	-0,237	-0,50—0,05	0,054
GLP-1	0,119	-0,10—0,38	0,341

The non-parametric data is presented as Spearman r and 95% CI. A *p*-value < 0,05 is considered statistically significant. * represents a *p*-value < 0,05; ** represents a *p*-value < 0,01; *p*-value < 0,001

Discussion

Overt T2DM is a complex metabolic condition involving various endocrine hormone interactions. Since hormones tend to fluctuate with ageing, the findings for this study are adjusted for ageing by only including participants between 25–45 years of age. It is unclear if the hormone dysregulations observed in T2DM will be seen in individuals with pre-diabetes between 25 – 45 years. Hence, this study highlights the various hormones linked with T2DM in persons with pre-diabetes.

C-peptide is a parameter for insulin sensitivity and insulin production. Therefore, in Fig. 1, it is unsurprising that high c-peptide levels were detected in the pre-diabetes participants. Another study showed increased concentrations of C-peptide detected in insulin-resistant individuals recently diagnosed with T2DM, which supports the study's C-peptide outcome in subjects with pre-diabetes [23]. In Table 3, c-peptide positively correlates with HbA1c, suggesting that c-peptide contributes to glycemic control. We speculate that C-peptides remain elevated chronically during pre-diabetes to compensate for insulin resistance. If insulin resistance is unattended during pre-diabetes, then the C-peptide levels will continue to rise and reach the levels observed in T2DM. Interestingly, in Table 2, the hormone insulin levels are higher but not statistically significant in pre-diabetes participants. This may indicate that the level of insulin resistance is still moderate in persons with pre-diabetes.

The incretin, glucose-dependent insulinotropic polypeptide (GIP) levels shown in Fig. 1 are significantly lower in the pre-diabetes group compared to the non-pre-diabetes group. The GIP hormone is critical in maintaining the glucose homeostatic range by stimulating beta-cell proliferation and insulin secretion [24]. Comparable results have been observed in studies using participants with T2DM, where the effectiveness of GIP is almost completely lost [25, 26]. A meta-analysis study on individuals with T2DM showed that higher glycated haemoglobin (HbA1c) concentrations and ageing were linked with reduced GIP responses [27]. However, the results of this study reveal that the decrease in GIP levels begins at the pre-diabetic stage. We speculate that sustained low levels of GIP may be necessary to trigger the onset of hyperglycaemia and, in turn, T2DM. During the pre-diabetes phase, the low levels of GIP may be compensated by another incretin hormone known as GLP-1 to keep glucose levels below the T2DM diagnosis threshold.

The concentrations of GLP-1 in Fig. 1 remained relatively the same between the two groups, as no statistical significance was observed. A prospective study by Hoffmann et al.

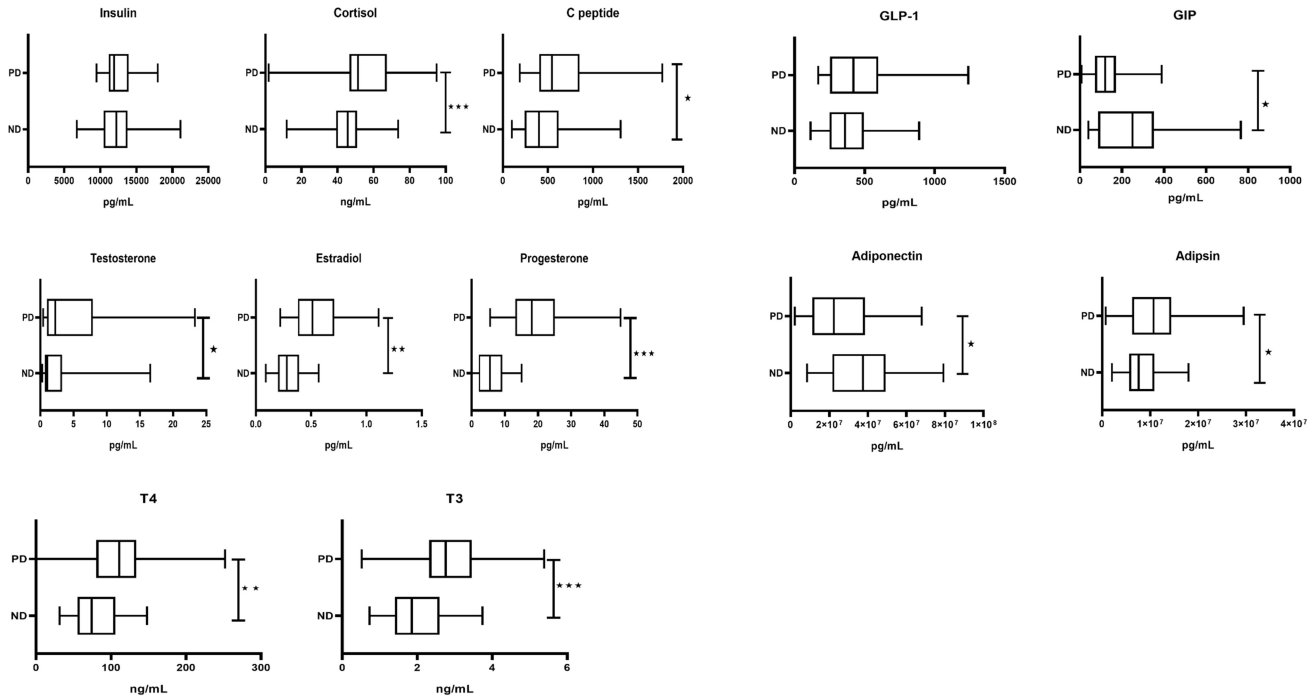

Fig. 1 Hormone concentration changes observed between the PD and ND groups. (Values are presented as mean ± 95% CI for parametric data or median ± IQR for non-parametric. ★ (ND vs PD, $p < 0.05$); ★★ (ND vs PD, $p < 0.01$); ★★★ (ND vs PD, $p < 0.001$))

(2023) also detected no changes in GLP-1 levels at the pre-diabetes state, but a decline in GLP-1 concentrations was seen in patients progressing to diabetes [28]. Therefore, it is plausible that the imbalance of GLP-1 may be a triggering point for the development of T2DM. Therefore, a longitudinal study is warranted to investigate the role of both GIP and GLP-1 in the progression from pre-diabetes to T2DM. A clear understanding of their roles in developing pre-diabetes and its passage to T2DM can play a pivotal role in introducing new therapeutic medications for pre-diabetes patients.

The cortisol concentration in Fig. 1 is significantly higher in individuals with pre-diabetes when compared to those in the non-pre-diabetes group. In Table 3, a positive correlation between cortisol and HbA1c was determined. Elevated cortisol levels have been shown to promote disturbance in glucose homeostasis by inducing visceral fat accumulation, reducing insulin sensitivity in skeletal muscles, and causing lipolysis. The reduction in insulin sensitivity may be exacerbated by the significantly lower levels of the hormone adiponectin. Studies have linked the decrease of adiponectin with insulin resistance and T2DM [29, 30]. Moreover, dysregulation of adiponectin has been observed in non-obese individuals, indicating its potential utility in studies where BMI data is unavailable. [31]. Therefore, adiponectin may be one of the critical causes and markers of interest that promote glycaemic dysregulation, resulting in pre-diabetes and T2DM if left unattended. However, the adverse complications of high cortisol and low adiponectin levels seen in pre-diabetes may be attenuated by the significantly elevated adipsin levels. The hormone adipsin is responsible for sustaining adipose tissue homeostasis and boosts insulin secretion in response to glucose [32]. Hence, adipsin is associated with protection from T2DM and may be one of the key compensatory mechanisms that delay pre-diabetes progression to overt diabetes. However, a longitudinal study that will adjust for the confounding variable, body weight, and trace adipsin levels from pre-diabetes to T2DM is necessary to have a conclusive statement.

The role of sex hormones in T2DM is well-documented [33–35]. Their role in pre-diabetes remains limited. The risk of developing diabetes is more significant in men with low testosterone [36]. In females, however, high testosterone concentrations were associated with an elevated risk of diabetes onset [37]. In Table 3, this study observed no significant changes in testosterone levels in the male groups. This suggests that in males aged 25–45 with pre-diabetes, the testosterone levels are not yet dysregulated and may decrease upon the onset of overt diabetes. This also suggests that the leading cause of testosterone drop observed in other studies may be ageing since testosterone levels are known to decrease with age [38]. In females, Table 3 results show that testosterone was higher in participants with pre-diabetes, which supports other literature findings that indicate a higher risk of diabetes in females with high

Table 3 Hormone changes stratified by gender

Hormone (units)	NPD	PD	*p* value
GIP (pg/mL)			
Male, median (IQR)	125,0 (80,3—296,2)	123,8 (100,1–290,8)	$p=0,7438$
Female, mean (95% CI)	355,7 (235,7–475,7)	126,6 (78,97–174,2)	$\mathbf{p=0,0055}$
C-peptide (pg/mL)			
Male, mean (95% CI)	675,8 (208,1–1144)	502,0 (372,7–631,3)	$p=0,3742$
Female, mean (95% CI)	476,7 (339,6–613,8)	886,3 (623,8–1149)	$\mathbf{p=0,0051}$
Insulin (pg/mL)			
Male	12,801 (10,492–15110)	12,451 (11,436–13,466)	$p=0,7406$
Female	11,969 (11,081–12858)	12,382 (11,525–13,239)	$p=0,4997$
GLP-1 (pg/mL)			
Male	415,6 (265,9–565,4)	469,0 (279,8–658,1)	$p=0,6559$
Female	369,1 (287,1–470,0)	466,4 (310,9–635,4)	$p=0,1892$
Adiponectin (ng/mL)			
Male, mean (95% CI)	32,835,6 (22,953–42,718,2)	26,818,3 (18,318–35,318,5)	$p=0,3316$
Female, mean (95% CI)	38,926,4 (30,462,3–47,390,4)	26,224,5 (18,018,4–34,430,6)	$\mathbf{p=0,0324}$
Adipsin (ng/mL)			
Male, mean (95% CI)	7272,7 (6014,5–8530,9)	17,284,5 (10,925,3–23,643,7)	$\mathbf{p=0,0183}$
Female, mean (95% CI)	9266,8 (7206,7–11,326,9)	11,602,1 (7860,3–15,344,8)	$p=0,2370$
Cortisol (ng/mL)			
Male, mean (95% CI)	50,4 (44–56,9)	61,9 (53,8–70,1)	$\mathbf{p=0,0455}$
Female, median (IQR)	42,9 (37,3- 47,9)	49,6 (41,4- 63,7)	$\mathbf{p=0,0232}$
Estradiol (ng/mL)			
Male, median (IQR)	0,39 (0,25–0,44)	0,570(0,42–0,83)	$\mathbf{p=0,0007}$
Female, mean (95% CI)	0,27 (0,2–0,3)	0,5(0,4–0,6)	$\mathbf{p=0,0001}$
Progesterone (ng/mL)			
Male	7,6 (4,5–10,7)	18,9 (13,9–23,9)	$\mathbf{p=0,0030}$
Female	5,5 (3,5–7,5)	20,6 (16,2–24,9)	$\mathbf{p=<0,0001}$
Testosterone (ng/mL)			
Male, mean (95% CI)	7,8 (4,62–10,96)	8,6 (6,2–11,1)	$p=0,6518$
Female, mean (95% CI)	0,9 (0,7–1,1)	1,2(0,9–1,5)	$\mathbf{p=0,0344}$
T3 (ng/mL)			
Male, mean (95% CI)	1,8 (1,4–2,2)	2,7 (2,3–3,1)	$\mathbf{p=0,0026}$
Female, median (IQR)	2,1 (1,5- 2,7)	2,8 (2,5- 3,5)	$\mathbf{p=0,0036}$
T4 (ng/mL)			
Male	70 (47,2–92,7)	106,4 (87,9–124,9)	$\mathbf{p=0,0133}$
Female	86,9 (75,5–98,4)	120,9 (92,9–149,0)	$\mathbf{p=0,0116}$

Parametric and non-parametric data are presented as mean ± 95% CI and median ± IQR. A $p<0.05$ is regarded as statistically significant

testosterone levels. The other sex hormone investigated is estradiol. Estradiol has a protective impact on the insulin β cells. Compared to the control group, females with pre-diabetes have higher estradiol levels. This may explain why the proportion of females with pre-diabetes is less when compared to males. There is literature evidence showing an increased incidence of diabetes in females who have reached menopause. Estradiol deficiency occurs after menopause, increasing the risk of T2DM onset [39]. Therefore, maintaining the homeostatic range of estradiol may be part of the compensatory mechanisms responsible for preventing T2DM and opens the door for designing new therapeutic targets [40].

Triiodothyronine (T3) and tetraiodothyronine (T4) levels were significantly elevated in the pre-diabetes group and correlated with HbA1c levels, indicating a proportional relationship between thyroid hormones and pre-diabetes onset. In literature, both hypothyroidism and hyperthyroidism have been shown to be associated with T2DM [41]. Hyperthyroidism has been reported to worsen glycaemic control in patients with T2DM. Therefore, it can be one of the essential hormones responsible for the progression from pre-diabetes

to T2DM over time [42]. Females are more susceptible to developing thyroid dysfunction than males [43]. The study observed the same trend for women with pre-diabetes in Table 3. However, the understanding of the association remains unclear and necessitates further investigation into the pre-diabetes condition. An intervention study targeting hyperthyroidism in women can be done on participants with diabetes and pre-diabetes to provide empirical evidence that will improve individualised care and management of diabetes.

The findings, although not yet conclusive, raise a question about possible alternative treatments to metformin, such as hormone replacement medications and GIP/GLP-1 agonists, which could be administered in persons with pre-diabetes. For example, a study by Iskra Bitoska et al. (2016) showed that hormone replacement therapy improves insulin sensitivity in women with T2DM [44]. A dual GIP/GLP-1 receptor co-agonist, Tirzepatide, has been sanctioned for managing T2DM. It is a modified acylated peptide that stimulates GIP and GLP-1 receptors [45]. These receptors play pivotal roles in insulin secretion and are also present in areas of the brain responsible for regulating food intake. These interventions may prove beneficial in the management of pre-diabetes; thus, preclinical trials are warranted.

Conclusion

The irregular hormonal changes of adipsin, thyroid, GIP, C-peptide, sex steroids, and cortisol hormones detected in pre-diabetes contribute to the growing body of research suggesting that pre-diabetes is an unfavourable metabolic condition. The study could not determine conclusively the causes of these imbalances due to the retrospective nature of the study as it lacked some confounding variable data, such as the subjects' weight. Adiponectin, C-peptide, progesterone, estradiol, T3, T4, and cortisol hormones exhibit correlations with HbA1c levels, indicating that persistent dysregulation of these hormones may disrupt glucose homeostasis and predispose individuals to the development of overt diabetes if left unaddressed. Hence, our study supports Bailey (2023) in the notion that it is never too early to intervene for pre-diabetes [10]. Subsequently, it opens a window for clinical trials investigating pharmacological interventions that would restore hormonal homeostasis, which may attenuate intermediate hyperglycaemia. However, prior to the intervention trials, future studies evaluating the mechanism behind the observed impairment in the hormonal control of adipokines, sex, and thyroid hormones are needed. In addition, a longitudinal study that tracks these hormone changes from the pre-diabetes phase to diabetes is necessary. Although surrogate markers for obesity were reported, the unavailability of data for other possible confounders was a limitation in the study, as it did not allow adjustment for confounding variables like BMI (Body Mass Index), diet, and physical activity. A future study with a larger sample size is recommended to generate results that can be generalised for the entire country and, in turn, validate our suggestion to consider incorporating these hormones in the screening processes to improve pre-diabetes care.

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Author contributions AMS and AK conceptualised the research, designed the study, and drafted the manuscript. AMS, NCM, AK and PSN were responsible for reviewing and approving the final draft of the manuscript.

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Declarations

Ethical approval The study was approved by the Ethics Committee of the University of KwaZulu Natal (Study ref: BE266/19) and was performed in line with the principles of the Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual study participants.

Conflict of interest The authors declare no conflict of interests.

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