Original Article

Cardiovascular Risk Factors in Sheehan's Syndrome: A Case-Control Study

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Abstract

Introduction: Obesity, dyslipidaemia and insulin resistance are associated with hypopituitarism. The association between these conditions and Sheehan's syndrome (SS) caused by post-partum pituitary gland necrosis is poorly understood. This study aimed to assess cardiovascular risk surrogate markers in SS patients, and we compared clinical, biochemical and radiological testing with healthy controls. **Methods:** In this cross-sectional study, we studied 45 patients with SS on standard replacement therapy and compared them with healthy controls. All subjects underwent anthropometric, inflammatory marker and hormonal measurement (adrenocorticotropic hormone (ACTH), stimulated cortisol, insulin-like growth factor-1 (IGF-1), thyroxine (T4), follicle-stimulating hormone (FSH), luteinising hormone (LH), oestradiol (E2), prolactin (Prl), insulin, interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP)). Carotid intima-media thickness (CIMT), flow-mediated dilation (FMD) and echocardiography were also performed. **Results:** The mean age and body mass index (BMI) of SS patients were 48.1 ± 10.0 years and 24.3 ± 4.3 kg/m^2, respectively, while those of controls were 44.6 ± 12.0 years and 24.6 ± 3.2 kg/m^2, respectively. Systolic blood pressure was significantly higher in SS (124.6 ± 20.8 vs. 117.0 ± 18.6 mm of Hg, $P < 0.05$). All SS patients were hypothyroid, and all except one were hypocortisolaemic. Triglyceride (TG) levels were significantly higher in SS patients (165.6 ± 83.3 vs. 117.2 ± 56.1, $P < 0.01$), but no difference in the prevalence of metabolic syndrome (MetS) was found. hs-CRP (9.1 (5.2–18.5) vs. 1.5 (0.6–2.8), $P < 0.001$) and IL-6 (4.9 (3.7–7.3) vs. 3.1 (2.0–4.2), $P < 0.001$) were significantly higher in SS patients. CIMT was significantly increased in SS patients, but no difference in FMD was found. Echocardiography revealed no significant difference in left ventricular (LV) dimensions, interventricular thickness, posterior wall thickness, ejection fraction, LV mass and diastolic function. **Conclusion:** SS patients show increased cardiovascular risk with hypertension, dyslipidaemia and increased atherosclerotic and inflammatory markers.

Keywords: Cardiovascular risk, dyslipidaemia, hypopituitarism, insulin resistance, metabolic syndrome, sheehan syndrome

Introduction

Sheehan's syndrome (SS) is an important cause of hypopituitarism in developing countries due to poor obstetrical care.[1] The post-partum haemorrhage leads to hypovolaemia and vasospasm, resulting in pituitary necrosis. SS patients have reported pituitary hormonal deficiency of growth hormone (GH) (100%), Prl (71-100%), corticotropin (71–87%), thyrotropin (73–90%) and gonadotropin (80–100%).[2-4]

Patients with pituitary hypofunction have an increased prevalence of conventional cardiovascular risk factors such as obesity, hypertension, glucose intolerance, dyslipidaemia, increased coagulability and insulin resistance.[5-8] All these factors, along with GH deficiency (GHD), predispose to metabolic syndrome (MetS) and increased cardiovascular morbidity.[5,9] It is also found that unphysiological steroid replacement and inadequate thyroxine and sex steroid replacement may contribute to this increased risk.[10-13] Inflammation plays a central role in the pathogenesis of atherosclerosis, and the likelihood of cardiovascular events has been shown to be predicted by serum inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP) and

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interleukin-6 (IL-6).[14] Women with hypopituitarism have elevated IL-6 and CRP levels.[15]

In addition, hypopituitary patients have been reported to have increased arterial intima-media thickness and an increased prevalence of atherosclerotic plaques and endothelial dysfunction.[15,16] A well-documented measurement of the endothelial function was flow-mediated brachial artery dilatation.[16-18]

The prevalence of MetS in India is high in the general Indian population in comparison with European Caucasians.[19] Features of glucose intolerance are evident at a younger age and lower body mass index (BMI).[20] Hence, it is possible that the combined effect of genetic predisposition to MetS, delay in diagnosis of SS, untreated GHD and over-treated with steroids might result in increased cardiovascular risk factors in SS.

There is little information on cardiovascular risk factors for SS subjects.[21] Accordingly, we studied various cardiovascular risk factors and markers of endothelial cell function including hs-CRP and IL-6, as well as functional abnormalities of the endothelium denoted by flow-mediated dilation (FMD) and carotid intima-media thickness (CIMT) along with cardiac dysfunction and structural changes by two-dimensional (2D) echocardiography in patients with SS.

Materials and Methods

Patients and controls

It was a cross-sectional case-control study conducted over 2.5 years (2018–2020). We recruited 45 patients having SS coming to the endocrinology outpatient department (OPD) of a tertiary care government referral centre. SS was diagnosed by a history of post-partum haemorrhage or amenorrhoea following childbirth or lactational failure, hormonal evaluation suggestive of loss of one or more pituitary hormone reserves and an absence of radiological feature of a pituitary mass.[22,23] Patients with a history of head injury, meningoencephalitis, pituitary adenomas or their surgery and head and neck irradiation were excluded. Patients with chronic illnesses such as liver or renal impairment were also excluded. Forty-five healthy women matched for age, sex and BMI with SS patients were recruited as controls from the community. None had a history of post-partum haemorrhage or amenorrhoea or lactational failure. The control subjects (age, sex and BMI matched) were from the same socio-economical strata and geographical region as the SS patients with no obvious medical illness.

Study protocol

Patients were interviewed using a structured pro forma. History, clinical parameters and anthropometric measurements, including height, weight, BMI, waist circumference (WC) and hip circumference (HC), were noted. Body weight (kilogram) was measured without footwear in light clothing and height without footwear or cap (centimetre), WC was measured with non-stretchable tape at the midpoint between the iliac crest and lower rib margin at the end of normal expiration, and HC was measured with non-stretchable tape at the widest level of the greater trochanters. BMI (in kg/m^2) was also calculated with the following formula:

BMI = weight (kilogram)/height (meter)^2

In patients of SS, fasting blood samples were collected for insulin-like growth factor-1 (IGF-1), thyroxine (T4), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), luteinising hormone (LH), oestradiol (E2) and Prl. Stimulated serum cortisol, taken 1 h after intramuscular injection of 250 µg synthetic aqueous ACTH (Synacthen®, Mallinckrodt, Dublin, Ireland), was measured in SS patients.

For patients of SS and healthy controls, fasting samples for the estimation of serum insulin level, IL-6 and hs-CRP were separated and stored at -80°C until assayed. An oral glucose tolerance test (OGTT) was performed as per American Diabetes Association (ADA) recommendation using 75 gm of anhydrous glucose and collecting blood samples after 2 hours in a fluoride vial.[24] Lipid parameters such as total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and very LDL (VLDL) were also estimated from the same fasting sample.

CIMT and FMD were measured by a team of radiologists (SS and SK), while 2D echocardiography was performed by cardiologists (KC and NG), who were blinded to patients and controls.

The CIMT of both common carotid arteries was measured 1 cm proximal to the bifurcation. The distance between the junction of lumen and intima and the junction of media and adventitia of both common carotid arteries was measured. The average of three measurements was taken during the end of the diastole on each side, and the mean of both, left and right, sides was taken for an overall CIMT.[25]

In FMD, the diameter of the brachial artery, 5–8 cm proximal to the bifurcation, was measured in the end-diastole phase, as the average of three readings and the same reference point was used for repeating measurement after 3–5 minutes of inflating above systolic pressures for 5 minutes, followed by deflating a blood pressure cuff. Upon the release of the pressure of the cuff, an increase in shear stress results in an endothelial-dependent nitric oxide release, which leads to brachial artery dilatation.[26]

2D echo was performed to assess left ventricular (LV) dimensions and volumes, posterior wall thickness, interventricular septum thickness, LV ejection fraction, aortic diameter and left atrial diameter and trans-mitral early/atrial peak velocity ratio (e/a). The LV mass was calculated using the following formula: LV mass = 1.04 ((LV end-diastolic diameter+interventricular wall thickness+posterior wall thickness) ^{3}-(LV end-diastolic diameter)^3)-13.6 g.[27]

Magnetic resonance imaging (MRI) of the sellar and suprasellar regions was performed using the Signa HD×t 3.0T platform (Wipro GE Healthcare, India). Echocardiography with colour Doppler was performed using GE Vivid E9 XD Machine (Waukesha, Wisconsin, USA).

Definitions

SS was diagnosed by a history of post-partum haemorrhage followed by absent lactation or menstrual disturbances, clinical and laboratory evidence of deficiency of one or more pituitary hormones and an absence of radiological features of other causes of hypopituitarism.[2]

Impaired fasting glucose (plasma glucose 100–125 mg/dL), impaired glucose tolerance (2-hour plasma glucose of 140–199 mg/dL after oral glucose tolerance test) and diabetes mellitus (fasting plasma glucose ≥126 mg/dl and 2-hour plasma glucose ≥200 mg/dl) were defined according to ADA criteria.[24]

MetS was defined using the National Cholesterol Education Programme or Adult Treatment Panel (NCEP or ATP III).[28] Accordingly, MetS in females is defined as the presence of three or more of the following: WC ≥80 cm, blood pressure ≥130/85 mmHg, TG level ≥150 mg/dl, HDL <50 mg/dl and fasting plasma glucose ≥100 mg/dl.

Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). It was calculated as fasting glucose (mg/dL) × fasting insulin (μIU/mL)/405.[29] HOMA%S and HOMA%β (which were used to measure insulin sensitivity and β-cell function) were calculated using the HOMA 2 Calculator v 2.2.3 (http://www.dtu.ox.ac.uk/homacalculator/).[30] Hypocortisolism was defined by peak serum cortisol <480 nmol/l after short synacthen test (SST) and/or undetectable cortisol along with low or normal ACTH.[31] GHD was defined as serum IGF-1 levels that were 3 SD lower than the age- and gender-defined lower range for healthy women.[32,33] Secondary thyroid hormone deficiency was diagnosed by low T4 (<58 nmol/l) and low or normal TSH values and E2 deficiency by low serum E2 (<99 pmol/l) and low or normal FSH.[34,35]

The e/a ratio: It is the ratio of peak velocity blood flow from LV relaxation in early diastole (the E wave) to peak velocity blood flow from atrial contraction in late diastole (the A wave).[36]

Assays

Serum biochemistry (lipid profile and blood glucose) was performed on an auto-analyser (Imola Randox, Ramsey, MN). The minimum detectable concentration with acceptable precision was 33.4 mg/dL, 11.9 mg/dL, 7.3 mg/dL and 11.9 mg/dL for TC, LDL, TG and HDL, respectively. IGF-1 (analytical sensitivity 0.6 nmol/l) was measured by immunoradiometric assay (Beckman Coulter, Brea, CA). Serum cortisol was measured by radioimmunoassay (RIA) (Diagnostic Product Company, Siemens, Washington DC, USA) between 2006 and 2009 (analytical sensitivity 5.5 nmol/L) and subsequently by a chemiluminescence assay (Immulite 1000, Siemens, Erlangen, Germany; analytical sensitivity 5.5 nmol/L). Plasma ACTH was initially measured by immunoradiometric assay (IRMA) (DSL, Beckman Coulter, Brea, CA, USA; analytical sensitivity 0.31 pmol/L) and, from 2016 onwards, by electrochemiluminescence (cobas e411, Roche, Basel, Switzerland; analytical sensitivity 0.22 pmol/L). T4, TSH, E2, LH, FSH and Prl were measured using a chemiluminescence analyser (Immulite 1000, Siemens, Germany). Insulin, IL-6 and hs-CRP were measured using a chemiluminescence analyser (Immulite 1000, Siemens, Germany). The assays had analytical sensitivity as follows: insulin (0.2 μU/Ml), IL-6 (2 pg/mL) and hs-CRP (0.1 mg/L).

Statistical analysis

The questionnaires were coded and entered, and data were analysed. The Shapiro-Wilk test was used to determine the normality of the data. Descriptive statistics were presented by summarising continuous variables in mean ± standard deviation or median (interquartile range 'IQR') and categorical variables by frequency and percentage. An independent-samples *t*-test was used for normally distributed parameters such as age, BMI, waist-to-hip ratio (WHR), TC, HDL and LDL, while the Mann-Whitney test was used to compare non-normally distributed clinical and biochemical parameters such as systolic blood pressure (SBP), fasting blood sugar (FBS), OGTT and TG and radiological parameters such as CIMT and FMD.

The prevalence of dyslipidaemia, MetS, IGT, diabetes and hypertension was calculated, and the Chi-square test was used to calculate the differences in these parameters between cases and controls. Linear regression analysis was performed for inflammatory markers such as hs-CRP and IL-6 with variables including age, WHR, FBS, TC, TG, LDL-C, HOMA%Beta, HOMA-IR, HOMA%S, CIMT, FMD and LV mass. The difference was considered statistically significant at $P < 0.05$. Statistical Package for Social Science, version 23 (IBM, Chicago, USA), was used for data analysis.

Ethical aspects

Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The privacy rights of human subjects were observed. All research procedures were performed according to the criteria set out in the Helsinki Declaration of 1964, as revised in 2000. The study was approved by the Institutional Ethics Committee of the Institute (2018-49-IMP-EXP, dated 13 April 2018).

Results

Sheehan patient's clinical and biochemical characteristics

A total of 45 patients in this study had all been diagnosed with SS and were being followed up on. The patients had an age of 48.1 ± 10 years and belonged mainly to the middle (77%) and lower (12%) socioeconomic strata.[37] Their age at last delivery was 27.7 ± 4.4 years (range 18–38 years), and the median (IQR) duration of illness was 20 years (12.5–24.5 years) [Table 1]. The median duration of delay in diagnosis was 10 years. Twenty-nine (64%) patients had home deliveries, and 36 (80%)

Table 1: Baseline clinical and biochemical characteristics of Sheehan patients (n=45)

Variables	Patients
Age (years)	48.1±10.0
BMI (kg/m^2)	24.3±4.3
Age of menarche (years)	13.8±1.1
Duration of hypopituitarism (years)	20 (12.5–24.5)
Age of PPH (years)	27.7±4.4
Lactation failure	42 (93.3)
Secondary amenorrhoea	44 (97.8)
History of adrenal crisis	23 (51.1)
Duration of thyroxine intake (years)	7 (3–14)
Duration of glucocorticoid intake (years)	7 (2–10.5)
Duration of sex steroid replacement (years)	2 (0–6)
Total T4 (nmol/L)	51.3±38.7
Prolactin (mIU/L)	109.6±153.5
E2 (pmol/L)	94.0±71.4
LH (IU/L)	3.9±7.6
FSH (IU/L)	5.3±6.1
8 AM cortisol (nmol/L)	60.5±75.7
Stimulated cortisol (nmol/L)	150.3±181.9
ACTH (pmol/L)	1.92±2.9
IGF-1 (nmol/L)	4.0±3.5

BMI=body mass index, PPH=post-partum haemorrhage, HDL=high-density lipoprotein, total T4=total thyroxine, E2=oestradiol, LH=luteinising hormone, FSH=follicle-stimulating hormone, ACTH=adrenocorticotropic hormone, IGF-1=insulin growth factor-1. Values were expressed as *n* (%) or mean±SD or median (IQR). *T4 and E2 (performed in 29 patients) values before replacement, #no patient on growth hormone replacement. Reference ranges: T4: 58–162 nmol/l, prolactin: 102–496 mIU/L, serum IGF-1: according to age and sex, serum cortisol 1 h after a short ACTH stimulation: >500 nmol/l, ACTH: 1.6–13.9 pmol/L, oestradiol: follicular phase: 76–587 pmol/L, luteal phase: 101–905 pmol/L

had a history of post-partum haemorrhage. There was a history of secondary amenorrhoea in 44 (98%) patients. At the time of presentation, 42 (93%) patients had lactational failure, and half had a history of adrenal crisis.

At the time of presentation, all SS patients were hypothyroid, and during the study, they were undergoing thyroxine replacement for a median duration of 7 (IQR 3–14) years. The replacement dose of levothyroxine ranged from 1.5 to 1.8 micrograms per kilogram (75-100 µg/day). Except for one patient, all were hypocortisolaemic and were receiving replacement therapy, with a median duration of 7 (IQR 2–10.5) years. Patients were taking hydrocortisone at a dose of 8 mg/m^2 body surface area (BSA)/day in three divided doses or prednisolone at a dose of 2.5–3.75 mg/day in two divided doses. Of the participants, eleven were new referrals to our clinic, while 34 had been previously monitored. Twenty-nine (32%) patients received oral cyclical E2 and progesterone (ethinyloestradiol 30 µg and levonorgestrel 150 µg) (Ovral L, Wyeth, Mumbai, India) for varying durations. In this study, the mean IGF-1 level was 4.0 ± 3.5 nmol/L, and no patients were undergoing GH therapy [Table 1]. All patients denied having smoked or consumed alcohol in the past.

MetS, diabetes lipid and insulin sensitivity parameters in SS vs. controls

We also recruited 45 age-, sex- and BMI-matched healthy controls from the community. The clinical and biochemical parameters of both groups are shown in Table 2. The mean age of Sheehan patients was 48.1 ± 10.0 years, while that of controls was 44.6 ± 12.0 years (P = 0.13). The BMI of cases and controls was 24.3 ± 4.30 kg/m^2 and 24.6 ± 3.18 kg/m^2 (P = 0.71), respectively. There was a significant difference in WHR of cases and controls (0.95 ± 0.08 vs. 0.89 ± 0.07, P < 0.001). Hypertension was significantly higher in SS as compared to controls (31.1% vs 8.9%, P < 0.01). Systolic blood pressure was significantly higher in SS (124.6 ± 20.8 vs. 117.0 ± 18.6 mm of Hg, P < 0.05). The difference in the prevalence of DM was not significant (31.1% vs. 13.3%, P = 0.05). Similarly, the difference in the prevalence of MetS was statistically non-significant in SS as compared to controls (32.5% vs. 27.9%, P = 0.4). TG levels were significantly higher in patients with SS than in controls (165.6 ± 83.3 vs. 117.2 ± 56.1, P < 0.01) but no difference in TC, HDL-C and LDL-C was found.

There was no significant difference in insulin resistance and insulin sensitivity in SS patients as compared to healthy controls.

Inflammatory markers, CIMT, FMD and 2D echocardiography in SS vs. controls

SS patients had significantly higher hs-CRP (9.1 (5.1–18.5) vs. 1.5 (0.6–2.8), P < 0.001)) and IL-6 (4.9 (3.7–7.3) vs. 3.1 (2.0–4.2), P < 0.001) as compared to controls.

CIMT was significantly increased in SS as compared to controls (0.62 ± 0.11 vs. 0.57 ± 0.14, P < 0.05). There was no difference in FMD values between the cases and controls (20.0 ± 9.9 vs. 19.4 ± 6.6, P = 0.80). On echocardiography, there was no valvular or endocardial defect in any patients, and none showed any pericardial defect. Ten (25%) patients had diastolic dysfunction as suggested by the e<a ratio, and it was not significantly different as compared to controls (10 (22.2%) vs. 7 (15.6), P = 0.28). There was no significant difference in LV dimensions, interventricular thickness, posterior wall thickness, ejection fraction and LV mass. None of the SS patients had echocardiographic findings suggestive of pulmonary vascular involvement [Table 3]. On multivariate regression analysis, hs-CRP and IL-6 were not associated with age, BMI, insulin resistance, mean CIMT, mean FMD, TC, TG, LDL and HDL [Table 4].

Discussion

SS remained a common cause of hypopituitarism in developing countries, and diagnosis was frequently delayed due to non-specific symptoms.[38] Recent studies have found an increase in cardiovascular mortality in patients with long-term untreated hypopituitarism.[15] GHD was associated with accelerated atherogenesis, in addition to

Table 2: Comparison of clinical and biochemical characteristics of Sheehan patients and healthy controls

Patients	Patients (*n*=45)	Controls (*n*=45)	*P*
Age (years)	48.1±10.0	44.6±12.0	0.13
BMI (kg/m^2)	24.3±4.3	24.6±3.2	0.71
Waist-to-hip ratio	0.95±0.08	0.89±0.07	<0.001
Hypertension	14 (31.1)	4 (8.9)	<0.01
Metabolic syndrome	18 (41.9)	14 (32.6)	0.50
Dysglycaemia (IGT + DM)	20 (44.4)	12 (26.7)	0.06
Triglycerides (mg/dl)	165.6±83.3	117.2±56.1	<0.01
Low-density lipoprotein (mg/dl)	111.0±36.2	115.5±26.6	0.5
hs-CRP (mg/l)	9.1 (5.2–18.5)	1.5 (0.6–2.8)	<0.001
Interleukin-6 (pg/ml)	4.9 (3.7–7.3)	3.1 (2.0–4.2)	<0.001
HOMA-IR	1.7 (0.6–4.4)	2.3 (1.6–3.6)	0.15
HOMA%β	103.9 (62.1–161.2)	94.7 (70.7–151.4)	0.69
HOMA%S	106.6 (47.4–292.6)	91.8 (62.2–127.1)	0.26

IGT=impaired glucose tolerance test, DM=diabetes mellitus, hs-CRP=high-sensitive C-reactive protein, HOMA-IR=homeostatic model assessment for insulin resistance, HOMA%S=homeostatic model for assessment of insulin sensitivity, HOMA%β=homeostatic model assessment for beta-cell function. Values were expressed as *n* (%) or mean±SD or median (IQR)

Table 3: Comparison of radiological and echocardiography parameters of Sheehan's syndrome patients with controls

Parameters	Patients (*n*=45)	Controls (*n*=45)	*P*
Carotid intima-media thickness (mm)	0.62±0.11	0.57±0.14	<0.05
Flow-mediated dilation (%)	20.0±9.9	19.4±6.6	0.80
Left ventricular mass (g)	155.9±42.2	153.1±43.5	0.77
Left ventricular dimension in systole (mm)	25.6±4.0	25.2±3.7	0.65
Left ventricular dimension in diastole (mm)	41.3±4.2	41.5±3.7	0.85
Interventricular thickness (mm)	10.0±1.5	10.0±1.3	0.88
Posterior wall thickness (mm)	10.0±1.4	9.7±1.4	0.30
Left atrial diameter (mm)	28.5±5.2	27.9±3.8	0.58
LV ejection fraction (%)	60.0±4.8	61.3±5.5	0.28
Trans-mitral e/a ratio	1.2±0.43	1.3±0.40	0.14
Diastolic dysfunction	10 (22.2%)	7 (15.6%)	0.28

e/a ratio=early/atrial peak velocity ratio, e/a ratio (it represents the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave)). Values were expressed as *n* (%) or mean±SD

traditional cardiovascular risk factors such as central obesity, insulin resistance and dyslipidaemia.[39] Furthermore, glucocorticoid (GC) over-replacement and a lack of sex steroids contribute to impaired metabolic parameters and atherogenesis in patients with hypopituitarism.[40,41]

Therefore, in this study, we looked at clinical, biochemical and radiological markers of cardiovascular risk, such as MetS, lipid profile, insulin resistance, hs-CRP, IL-6, CIMT, FMD and echocardiography in SS patients. In our study, we found increased cardiovascular risk factors, including hypertension, dyslipidaemia, central obesity, inflammatory markers such as hs-CRP and IL-6 and atherosclerotic markers such as CIMT present in SS patients.

The MetS is a group of interconnected metabolic risk factors that accelerate the progression of atherosclerotic cardiovascular disease. Patients with MetS had an approximately three- to fivefold higher risk of developing diabetes, two to three times higher risk of stroke or myocardial infarction (MI) and two times higher risk of all-cause mortality.[42,43] MetS prevalence ranged from 38 to 46% in hypopituitary adults and 15% in controls using NCEP or ATP III criteria in different series.[5] In a study from Kashmir, the prevalence of MetS in SS was 40% in SS, which was significantly higher than the controls.[21] Our study had a higher prevalence of MetS in SS (33%) as compared to controls (28%) although it did not meet the statistical significance. This may be due to the higher prevalence of MetS in the Indian population.[19]

Various studies in patients with hypopituitarism have revealed abnormality in lipid parameters, including increased TC, LDL-C, TG levels and normal or decreased HDL-C.[44] Despite thyroxine and GC replacement, patients with SS have adverse lipid parameters. In a study on 30 SS patients, TC, LDL-C and TGs were significantly raised.[21] Another study on SS revealed significantly higher TC, LDL-C and TG and low HDL levels.[45] Our study also documented increased TGs in SS patients. These lipid abnormalities were caused by chronic GHD, and GH replacement improves these lipid abnormalities.[13,46]

Table 4: Regression analysis of inflammatory marker (hs-CRP and IL-6) in Sheehan's patients

Variables	Multivariate (hs-CRP)		Multivariate (IL-6)	
	Beta-coefficient	*P*	Beta-coefficient	*P*
Age	0.08	0.66	0.7	0.75
BMI	-0.09	0.63	0.07	0.89
Waist-to-hip ratio	0.45	<0.01	0.36	<0.05
Fasting blood glucose	0.32	<0.05	0.14	0.62
LDL cholesterol	0.02	0.90	0.25	0.12
Triglyceride	-0.20	0.22	-0.19	0.24
HDL	-0.20	0.18	0.10	0.59
HOMA-IR	-0.62	0.11	-0.1	0.75
HOMA%Beta	0.07	0.65	0.15	0.36
HOMA%S	0.22	0.17	-0.06	0.79
Mean CIMT	-0.22	0.17	-0.07	0.78
Mean FMD	0.11	0.48	0.12	0.46
LV mass	0.06	0.74	-0.03	0.90
IL-6	-0.08	0.62	-	-
hs-CRP	-	-	-0.16	0.48

CIMT=carotid intima-media thickness, FMD=flow-mediated dilation, HOMA-IR=homeostatic model assessment for insulin resistance, HOMA%S=homeostatic model for assessment of insulin sensitivity, HOMA%β = homeostatic model assessment for beta-cell function, LDL=low-density lipoprotein, HDL=high-density lipoprotein, BMI=body mass index, hs-CRP=high-sensitivity C-reactive protein, IL-6=interleukin-6, LV mass=left ventricular mass

In the KIMS-Pfizer International Metabolic Database, 6050 hypopituitary patients were studied, and the prevalence of DM was 9.3% and was significantly increased in females. It also correlated with age, family history of diabetes, BMI, WC, GHD aetiology and number of pituitary deficiencies.[47] In a previous study on SS, the prevalence of IGT was 26.7%, which was higher than the controls, but no significant difference was found in the prevalence of DM.[21] In our study, 44% of subjects of SS had dysglycaemia, but there was no statistical difference in the prevalence of dysglycaemia or diabetes mellitus as compared to the control. This might be because of the late diagnosis of SS and the high prevalence of dysglycaemia in our region.

Despite being BMI-matched controls, WHR was significantly higher in SS. A prospective study from Liverpool of 152 patients with hypothalamic-pituitary disease found central adiposity in 86% and higher WC and WHR.[48] In a study of 40 hypopituitary patients, significantly higher WC and WHR were found and WC was associated with GH deficiency.[49] GHD leads to enlarged adipocytes and abdominal obesity, even with comparable BMI.[50]

Atherosclerosis is a disease of lipid accumulation and a chronic inflammatory process. Markers of chronic low-grade inflammation, such as hs-CRP and IL-6, could help assess cardiovascular risk.[51] hs-CRP levels have been linked to a poor cardiovascular prognosis and have been shown to predict the development of type 2 diabetes, hypertension and MetS.[52-54] Our study showed significantly higher hs-CRP in SS. The Multiple Risk Factor Intervention Trial (MRFIT) showed a strong relationship between levels of hs-CRP and mortality from cardiovascular disease.[55] In a Women's Health Study (WHS), LDL-C was compared with hs-CRP in 27,939 healthy women who were followed for an average of 8 yrs, and hs-CRP was a stronger predictor of cardiovascular disease (CVD) than LDL-C after adjustment for age and conventional risk factors.[56]

IL-6 is a pro-inflammatory cytokine that increases the production of acute-phase reactants in the liver, such as CRP.[57] We found significantly higher IL-6 in SS. IL-6 and CRP are increased in hypopituitary patients with untreated GHD in both men and women, and increased IL-6 levels were independently related to their CIMT.[58]

CIMT was a non-invasive imaging technique used to detect atherosclerosis and served as a surrogate marker for cardiovascular disease. Independent of traditional risk factors, CIMT has been shown to be a predictor of future cardiovascular events.[59] CIMT in SS was significantly increased in our study. Similarly, in a Turkish study, 40 hypopituitary patients, including those with SS, were evaluated and found to have significantly higher CIMT when compared to controls.[60] More importantly, a prospective intervention study on 35 GHD patients revealed that patients had significantly higher CIMT, which decreased after 5 years of GH replacement,[61] while a study by Elhadd *et al.* found no difference in CIMT in their 52 adult patients with hypopituitarism.[62] It was mainly due to the older age of patients and controls.

FMD has been documented to be a surrogate marker for measuring coronary endothelial function and a predictor of cardiovascular events.[63,64] We did not find a significant difference in FMD, which could be attributed to the fact that most of our patients were on hormonal replacement. A previous study on SS found lower FMD when compared to controls, and FMD increased significantly with treatment, implying that a combination of prednisolone, thyroxine and conjugated oestrogen may improve the efficacy of nitric oxide (NO) and endothelial dysfunction.[65]

Echocardiography with colour Doppler was a simple, non-invasive method of detecting structural changes in the heart. We did not find any significant difference in LV dimensions, ejection fraction or diastolic function. This could be because most of the patients were on thyroid and steroid replacement. A similar finding was reported by Laway *et al*. in their study of Sheehan's patients.[66] Previous studies conducted in hypopituitarism, especially GHD, showed a mixed picture, with some showing a decrease in diastolic function or systolic function while others having no structural abnormality.[67-69]

The strength of our study is a large number of patients of SS, and it was a case-control study where patients were matched for gender, age and BMI. The limitation of this study is that it is a cross-sectional study and patients were not followed up and no patient was on GH replacement.

Conclusion

This study demonstrated that SS patients on standard replacement therapy except GH replacement have increased cardiovascular risk, including hypertension, dyslipidaemia, central obesity, inflammatory markers such as hs-CRP and IL-6 and atherosclerotic markers such as CIMT, and may lead to increased mortality. It may be due to the long duration of oestrogen deficiency or GHD and unphysiological steroid replacement.

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None.

Authors' contribution

MA, SY, SKS, SK, KC, NG: Concepts, design, definition of intellectual content, clinical studies, data acquisition, data analysis, statistical analysis, manuscript editing and manuscript review MA, SY, SK, NG: Literature search, manuscript preparation SY: Guarantor.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Data can be made available after the request and due approval of Institute authority (SGPGI, Research Cell).

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