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Geographical/environmental effects on lipid profiles and its association with glycemic control in Saudi Arabia

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Chronic disease is one of the most prevalent health issues that affects a person's quality of life and is a serious problem that may affect the peoples around the world. In Saudi Arabia, the disease pattern has shifted from communicable to chronic disease in recent times. This study investigates the effect of geographical/environmental factors on the lipid profiles and their associations with blood pressure (BP) and HbA1c in the Saudi population residing at lowlands and highlands, respectively. Archived clinical data from the different commercial laboratories were screened for 18 months in Jeddah (lowland) and Asir (highland) regions of Saudi Arabia. Data were analyzed by SPSS statistics for the window. Small but significantly high blood pressure was observed in the study population from the Asir region compared to those from the Jeddah region ($p<0.05$). Prevalence of dyslipidemia was significantly high in the prediabetes and diabetes group of population ($p<0.05$) from the Jeddah region ($p<0.05$). Overall, prediabetes and diabetes were detected in 31.2% (2243) and 23.6% (1697). There were 12.3% prediabetic and 11.3% diabetic from the Asir region and 18.9% prediabetic and 12.2% diabetic from the Jeddah region ($p<0.05$). The clinical assessment of biochemical data revealed that the high prevalence of dyslipidemia is associated with prediabetes and diabetes in the Jeddah region (lowland). Furthermore, regression analysis suggested that dyslipidemia was associated with increased risk of prediabetes (OR, 95%CI=1.205, 1.068-1.359) and diabetes (OR, 95%CI= 1.93, 0.807-2.055). Furthermore, high blood pressure was associated with the population living at high altitudes.

Key words: Pre-diabetes, diabetes, dyslipidemia, highland, lowland, geographical/environmental effects.

INTRODUCTION

Diabetes is a rapidly growing public health problem with significant implications for human health, living standards, the economy, and healthcare systems worldwide. According to the International Diabetes Federation (IDF), approximately 463 million adults are living with diabetes globally, with this number expected to climb to 700 million by 2045 ('Diabetes Facts and Figures, 2021). According to a new report by the International Diabetes Federation,

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more than one in ten Saudis now have diabetes, and the disease's prevalence will increase in the Kingdom by 2045 (('Diabetes Facts and Figures, 2021). The IDF report found that 4.274.1 million people in Saudi Arabia, which has a population of about 34.8 million people, have diabetes. A further 1.863.5 million people have the disease but have not been diagnosed. Diabetes in Saudi Arabia is a problem that needs to be talked about quickly, openly, and honestly. The condition is slowly developing but progressive, and it can take many years for a person to progress from a prediabetic to a diabetic state if no interventions are implemented (Bahijri et al., 2016; Omar et al., 2021). Globally, the prevalence of diabetes is rising in lockstep with an increasing prevalence of dyslipidemia. Saudi Arabia and other Middle East regions have an exceptionally high prevalence of dyslipidemia associated with diabetes (Al-Nozha et al., 2004; Al Amri et al., 2019; Al-Hassan et al., 2018; Basulaiman et al., 2014; Enani et al., 2020; Al-Kaabba et al., 2012). According to the World Health Organization (WHO), Saudi Arabia has the second-highest diabetes rate in the Middle East and is seventh in the world (Al Dawish et al., 2016). Diabetes is often associated with dyslipidemia, which is widely recognized as an independent risk factor for diabetes (Zheng et al., 2017).

Diabetic dyslipidemia is characterized by the significant rise in fasting and postprandial triglycerides (TG), low-density lipoprotein (LDL), total cholesterol (TC), low level of high-density lipoprotein (HDL), and presence of small dense LDL particles (Wu and Parhofer, 2014). Patients with diabetic dyslipidemia are prone to develop the risk of coronary artery disease, stroke, peripheral vascular disease, nephropathy, retinopathy, and neuropathy (Alzahrani et al., 2019). The circulating level of glycated hemoglobin (HbA1c) is considered as the gold standard for glycemic control. It not only reveals blood sugar management but is also an essential factor in assessing the risk of diabetes-related complications (Alzahrani et al., 2019). Due to the diversity of environmental and lifestyle risk factors, the incidence of diabetes and dyslipidemia varies significantly by geographic location. Population living at highland has been reported to have a lower prevalence of diabetes and dyslipidemia than those at lowland (Woolcott et al. 2014; Woolcott et al. 2016; Villanueva et al. 2013; CedarsSinai 2021). The population from Jeddah and Asir region in Saudi Arabia has similar ethnic backgrounds, but they live at different altitudes. Jeddah is a Saudi Arabian port city on the bank of the Red Sea, with a population of about 4.7 million. It is situated 12 m above sea level ('Jeddah Population 2021 (Demographics, Maps, Graphs)' 2021). In Jeddah, summer is long and sweltering, and winter is short, warm, and dry. Typically, the temperature varies between 25 to 40° C throughout the year. Asir is situated 2,270 m above sea level in the South-western part of Saudi Arabia, with an estimated population of 2.2 million ('Population in Asir region by gender, age groups and nationality (Saudis / Non-Saudis) - Mid 2016 AD | General Authority for Statistics' 2017). Abha and Khamis-Mushayt are the two main cities of this region. The summers are long, hot, arid, and partly cloudy in the Asir region. The winters are short, cool, dry, and mostly clear ('Average Weather in Khamis Mushait, Saudi Arabia, Year Round - Weather Spark' 2021; 'Khamis Mushait climate: Average Temperature, weather by month, Khamis Mushait weather averages - Climate-Data.org'). Over the course of the year, the temperature typically varies from 9°C to 31°C and is rarely below 6°*C* or above 33°*C* ('Average Weather in Khamis Mushait, Saudi Arabia, Year Round - Weather Spark' 2021; 'Khamis Mushait climate: Average Temperature, weather by month, Khamis Mushait weather averages - Climate-Data.org').

In this study, we investigated the effects of geographical/environmental factors on the lipid profiles and their associations with BP and HbA1c in the Saudi population residing at different altitudes (low land and high land).

METHOD

Study design and subject

This is a cross-sectional population-based study conducted in Saudi Arabia during an 18-month period (January 2019-June 2020) between two indigenous communities living at different altitudes. This study utilized laboratory data consisting of lipid profile (TC, LDL, HDL, and TG) and HbA1c from the various commercial laboratories in Jeddah and Asir region, subjected to lipid profile and blood glucose analysis from January 2019 to June 2020. The data also include blood pressure assessment for the study population. A total of 6000 and 4500 lab reports were retrieved from records in Jeddah and Asir. After excluding incomplete lipid profiles and blood glucose reports, 4105 reports from Jeddah and 3095 reports from the Asir region were included in the final study. Laboratory investigations were reviewed and excluded for any abnormal renal, liver, or thyroid profiles. The screened population was either a customer who came to the lab for routine health check-ups or follow-up of chronic health conditions and was not sick.

Definition of variables

The reference range for TC was set as normal (< 200 mg/d), borderline high (200-239 mg/dL) and high (≥ 240 mg/dL) respectively ('Lipid Panel' 2021; healthline 2021). The reference range for LDL was set as optimal (< 100 mg/dL), near optimal (100-129 mg/dL), borderline high (130-159 mg/dL), high (160-189 mg/dL) and very high (≥ 190 mg/dL) respectively ('Lipid Panel' 2021; healthline 2021). The reference range for TG was set as normal (<150 mg/dL), borderline high (150-199 mg/dL), high 200-499 mg/dL and very high (≥ 500 mg/dL) respectively ('Lipid Panel' 2021; Healthline, 2021). For HDL the reference range was set as at risk (< 40 mg/dL), normal (40-60 mg/dL), optimal (> 60 mg/dL) respectively ('Lipid Panel', 2021; Healthline 2021). The cutoff point used for lipid profile parameters for TC was 200 mg/dL, TG was 150 mg/dL, LDL was 130 mg/dL, and HDL was 40 mg/dL respectively. Furthermore, we defined the dyslipidemia in our study as TC >200 mg/dl, LDL > 130 mg/dl, HDL < 35 mg/dl), or triglycerides >

Table 1. Baseline demographic characteristics of the study population.

Variable	Asir		Jeddah		*p-value**
	Male	Female	Male	Female	
Age (Median±IQR year)	50±27	41±25	49±20	46±23	0.000‡
Systolic BP (Mean±SD mm of Hg)	130.58±18.03	129.39±19.62	125.97±16.75	126.25±20.01	0.003‡
Diastolic BP (Mean±SD mm of Hg)	80.63±9.52	78.15±9.86	76.88±10.44	75.96±10.41	0.000‡
TC (Mean±SD mg/dL)	176.14±40.76	178.80±42.55	192.91±39.02	194.16±38.04	0.002†
LDL (Mean±SD mg/dL)	111.73±37.20	112.07±37.96	130.21±36.56	126.86±34.85	0.515†
TG (Mean±SD mg/dL)	128.81±85.78	116.37±64.64	139.78±83.05	113.80±60.34	0.000‡
HDL (Mean±SD mg/dL)	46.78±13.73	50.90±15.65	40.93±8.69	48.96±10.82	0.000‡
TC/HDL (Mean±SD mg/dL)	4.07±1.80	3.80±1.41	4.87±1.25	4.11±1.06	0.000‡
LDL/HDL (Mean±SD mg/dL)	2.57±1.14	2.40±1.08	3.28±1.05	2.70±0.93	0.000‡
HbA1c (Mean±SD mg/dL)	6.13±1.56	6.04±1.60	6.06±1.44	5.95±1.44	0.000‡
FBS(Mean±SD mg/dL)	107.71±18.51	104.96±21.43	129.50±25.39	127.91±24.60	0.000‡

*The level of statistical significance was set as $p < 0.05$. (†Independent sample T-test and ‡Mann-Whitney U test).

(150 mg/dl), or a combination thereof (Kavey et al., 2003). According to the last recommendation by American Heart Association (AHA) (Kim et al., 2019; 'Understanding Blood Pressure Readings' 2021), blood pressure (BP) were categories as normal (systolic(S) BP < 120 mm Hg and diastolic(D) BP < 80 mm of Hg), elevated (SBP = 120-129 mm of Hg and DBP < 80 mm of Hg), hypertension (HTN) stage 1 (SBP = 130-139 or DBP = 80-89 mm of Hg, HTN stage 2 (SBP > 140 mm og Hg or DBP > 90 mm of Hg) and hypertensive crisis (SBP > 180 mm of Hg and/ or DBP > 120 mm of Hg) ('Understanding Blood Pressure Readings, 2021; Kim et al., 2019). HbA1c was defined as normal if < 5.7%, prediabetes if 5.7%-6.4%, and diabetes if > 6.5% ('American Diabetes Association, 2021). Furthermore, HbA1c ≤ 7% was classified in our study as a good glycemic control and as non-glycemic control if HbA1c > 7% (Artha et al., 2019).

Statistical analysis

Data analysis was done using IBM-SPSS version 26 (SPSS Inc., Chicago, IL, USA). Chi-Square was used to analyze categorical variables and expressed as a percentage ± standard deviation (SD). The normality of the data was tested by the Kolmogorov-Smirnov test. Independent sample T-test and Mann-Whitney test were used to analyze two groups based on normally and non-normally distributed data. One-way analysis of variance (ANOVA) and Kruskal-Wallis test were used to assess the difference between group means of parametric and nonparametric variables, respectively. Spearman correlation was used to determine the correlation of lipid profile and lipid ratio to HBA1c in the study population. Logistic regression analysis and receiver operator characteristics (ROC) curves were used to make a risk analysis of lipid profile and lipid ratio against the risk prediabetes and diabetes in the study population living at different altitudes (Artha et al., 2019; Basit et al., 2020).

RESULT

General characteristics of the study population

This study sample consisted of 1667 (54.2%) males and 1419 (45.8%) females from the Asir region, and 1900 (46.3%) males and 2205 (53.7%) females from the Jeddah region with ages ranging from 17 to 91 years ($p < 0.05$). The median age interquartile range (IQR) of the study population from the Asir and Jeddah region was 46±27 and 46±21 years, and the most representative age group was above 50 years in both areas ($p < 0.05$). The mean systolic BP of the study population from the Asir and Jeddah region was 130.01±18.78 mm of Hg and 126.12±18.56 mm of Hg, respectively ($p < 0.05$). The mean diastolic BP of the study population from the Asir and Jeddah region was 76.46±10.44 mm of Hg and 79.29±9.78 mm of Hg, respectively ($p < 0.05$). SBP (±SD), DBP(±SD), TC (±SD), LDL(±SD), triglycerides (±SD), HDL(±SD), TC/HDL ratio ((±SD), LDL/HDL ratio (±SD) for study population from Asir and Jeddah region stratified by gender are presented in Table 1. From the baseline demographic characteristic of the study population, there was a significant difference ($p < 0.05$) in age, SBP, DBP, TC, TG, HDL, TC/HDL ratio, LDL/HDL ratio, and HbA1c in two regions stratified by gender. However, no significant difference ($p > 0.05$) was observed in the mean distribution of LDL between the study subjects of two areas stratified by gender (Table 1).

Prevalence of lipid profile and blood pressure

The mean age, systolic BP, diastolic BP, TC, LDL, TG, HDL, TC/HDL ratio, LDL/HDL ratio of the study population among normal, prediabetic, and diabetic groups in Asir and Jeddah regions are presented in Table 2. The significant difference (($p < 0.05$) in SBP, DBP, TC, LDL, TG, HDL, TC/HDL ratio, LDL/HDL ratio was observed between the groups with normal, prediabetes, and diabetes among the population living at lowland and high land respectively.

Total cholesterol

The prevalence of borderline high TC in the Asir region was 13.5% (630) in the prediabetes and 12.9% (601)

Table 2. Mean±SD of key variables at Asir (high altitude) and Jeddah (sea level).

Variable	Asir			Jeddah			*p* value
	Normal[1]	Prediabetes[2]	Diabetes[3]	Normal[1]	Prediabetes[2]	Diabetes[3]	
Age (Median±IQR years)	43±20	54±28	54±31	42±18	50±19	56±21	0.000‡
Systolic BP (Mean±SD mm of Hg)	125.11±16.99	131.73±18.45	136.65±19.7	122.26±17.16	127.47±18.16	132.17±20.09	0.000‡
Diastolic BP (Mean±SD mm of Hg)	75.06±10.13	77.32±10.63	80.56±10.10	77.93±10.44	78.05±9.60	80.17±9.63	0.000‡
TC (Mean±SD mg/dL)	173.59±44.85	178.06±38.41	179.74±43.13	191.02±41.19	192.62±35.89	196.53±39.94	0.000†
LDL (Mean±SD mg/dL)	107.28±39.57	114.45±39.86	112.81±34.49	124.56±37.36	128.47±33.45	130.82±37.31	0.000†
Triglycerides (Mean±SD mg/dL)	106.50±66.09	121.93±62.28	149.13±95.04	113.07±63.08	128.21±64.55	152.82±97.50	0.000‡
HDL (Mean±SD mg/dL)	50.77±15.46	48.45±13.51	45.33±14.28	46.71±10.87	45.06±10.33	42.44±10.16	0.000‡
Cholesterol/HDL (Mean±SD)	3.82±1.52	3.96±1.42	4.15±2.01	4.30±1.16	4.52±1.18	4.68±1.32	0.000‡
LDL/HDL (Mean±SD)	2.43±1.09	2.54±1.11	2.55±1.16	2.89±1.02	3.02±1.02	3.05±1.06	0.000‡
FBS (Mean±SD mg/dL)	85.95±2.35	107.99±4.53	146.42±21.31	96.25±4.13	115.78±7.55	236.42±17.32	0.000‡

[1]HbA1C <5.7, [2]HbA1c 5.7-6.4, [3]HbA1c ≥ 6.5. Analyzed by † ANOVA, ‡ Kruskal-Wallis test

diabetes group, while the prevalence of high TC among the prediabetes and diabetes group was 9.8% (70) and 9% (64) respectively ($p > 0.05$). Similarly, the prevalence of borderline high TC was 23.9% (437), 13.3% (224) for the prediabetes and diabetes group, while 26.8% (191) and 14.5% (103) was high TC in the prediabetes and diabetes group, respectively ($p < 0.05$) in Jeddah region. The prevalence of TC among the prediabetic and diabetic groups was significantly higher in the Jeddah region than in the Asir region ($p < 0.05$).

Low-density lipoprotein

In the Asir region, the prevalence of prediabetic and diabetic populations with borderline high LDL were11% (282) and 8.1% (142). In the Jeddah region, 22.2% (391) and 13.0% (244) population had borderline high LDL with prediabetic and diabetic, respectively. Among high LDL, 8.7% (70) and 8.3% (67) population from Asir region and 26.5% (213) and 13.8% (111) population from Jeddah region were prediabetic and diabetic respectively ($p < 0.05$). While 10.7% (31) and 7.2% (21) population from Asir region, and 28.4% (83) and 12.4% (36) population from Jeddah region with very high LDL were prediabetic and diabetic respectively ($p< 0.05$). The prevalence of prediabetic and diabetic population among the different category of LDL were significantly higher in the Jeddah region ($p<0.05$)

Triglycerides

The prevalence of borderline high TG with the prediabetic and diabetic group was 10.9% (106) and 17.5% (170) in the Asir region, and 20.2% (196) and 18.3% (183) Jeddah region, respectively ($p< 0.05$). Among High TG, 11.8% (90) and 17.8% (136) population were prediabetic and diabetic in the Asir region, and 21.4% (163) and19.3% (147) population from the Jeddah region were prediabetic and diabetic, respectively ($p < 0.05$). While 2.9% (1) and 41.2% (14) population from Asir region, and 5.9% (2) and 20.6% (7) population from Jeddah region with very high TG were diabetic and prediabetic respectively ($p > 0.05$). The prevalence of the population with borderline high and high TG with prediabetes and diabetes was significantly higher (p< 0.05) in the Jeddah region compared to the Asir region. However, no significant difference ($p < 0.05$) was observed among the population with very high TG.

HDL

In the Asir region, there was 10.1% (239) and 14.1% (333) population with prediabetic and diabetic respectively with HDL level at risk, while in the Jeddah region, it was 20.4% (483) and 17.4% (412), respectively ($p < 0.05$). The prevalence of prediabetic and diabetic populations among different HDL categories is significantly higher ($p < 0.05$) in the Jeddah region.

Prevalence of blood pressure

The prevalence of elevated BP in normal,

Table 3. Prevalence of lipid profile in Asir and Jeddah region.

Lipid		Asir			Jeddah			†*p* value
		Normal[1]	**Prediabetes**[2]	**Diabetes**[3]	**Normal**[1]	**Prediabetes**[2]	**Diabetes**[3]	
Cholesterol	Normal	22.2% (1036)	10% (182)	8.3% (151)	24.2% (1126)	15.7% (733)	11.5% (534	0.002
	Borderline high	14.7% (268)	13.5% (630)	12.9% (601)	29.9% (546)	23.9% (437)	13.3% (244)	0.014
	High	13.1% (93)	9.8% (70)	9% (64)	26.8% (191)	26.8% (191)	14.5% (103)	0.041
LDL	Optimal	24% (493)	15.6% (320)	18.9% (387)	16.8% (344)	13.2% (271)	11.5% (235)	0.016
	Near Optimal	21.5% (494)	11.7% (268)	8.7% (199)	29.4% (675)	17.6% (403)	11.1% (255)	0.043
	Borderline high	16% (282)	11% (193)	8.1% (142)	28.9% (509)	22.2% (391)	13.9% (244)	0.040
	High	12.2% (98)	8.7% (70)	8.3% (67)	30.5% (245)	26.5% (213)	13.8% (111)	0.012
	Very high	10.3% (30)	10.7% (31)	7.2% (21)	30.9% (90)	28.5% (83)	12.4% (36)	0.025
Triglycerides	Normal	21.8% (1182)	12.6% (685)	9.1% (496)	28% (1521)	18.4% (1000)	10.1% (550)	0.002
	Borderline high	11.8% (114)	10.9% (106)	17.5% (170)	21.3% (206)	20.2% (196)	18.3% (183)	0.000
	High	12.6% (96)	11.8% (90)	17.8% (136)	17.2% (131)	21.4% (163)	19.3% (147)	0.014
	Ver high	14.7% (5)	2.9% (1)	41.2% (14)	14.7% (5)	5.9% (2)	20.6% (7)	0.436
HDL	At risk	15% (354)	10.1% (239)	14.1% (333)	22.9% (541)	20.4% (483)	17.4% (412)	0.000
	Normal	17.7% (677)	12.7% (486)	9.7% (370)	29% (1109	20% (763)	10.8% (414)	0.000
	Optimal	35.9% (366)	15.4% (157)	11.1% (113)	20.9% (213)	11.3% (115	5.4% (55)	0.111
BP	Normal	20% (486)	8.1% (197)	5% (122)	36.5% (885)	20.1% (489)	10.2% (248)	0.009
	Elevated	9.5% (172)	12.1% (219)	21% (380)	11.2% (203)	19.3% (349)	26.9% (486)	0.049
	HTN stage 1	22.7% (287)	15.5% (196)	11.7% (148)	18.3% (231)	16.6% (209)	15.1% (191)	0.048
	HTN stage 2	14.5% (231)	16% (255)	16.4% (262)	15.4% (245)	18.5% (295)	19.2% (307)	0.033
	Hypertensive crisis	12.1% (13)	14% (15)	18.7% (20)	15% (16)	17.8% (19)	22.4% (24)	0.588

[1]HbA1C <5.7, [2]HbA1c 5.7-6.4, [3]HbA1c ≥ 6.5, † Analyzed by Chi-square test.

prediabetic and diabetic group was 9.5% (172), 12.1% (219) and 21% (380), respectively in Asir region, while in Jeddah region it was 11.2% (203) 19.3% (349) and 26.9% (486), respectively (p = 0.049). Similarly, the prevalence of HTN stage 1 and HTN stage 2 was significantly higher ($p < 0.05$) in the study population from the Jeddah region compared to the Asir region. The prevalence of hypertensive crisis in the Asir region in the normal, prediabetic, and diabetic group was 12.1% (13), 14% (15), and 18.7% (20), respectively, while in the Jeddah region, it was 15% (16), 17.8% (19) and 22.4% (24). There were no significant differences in the normal, prediabetic, and diabetic status between the Asir and Jeddah regions with hypertensive crisis (p = 0.588).

A descriptive analysis of the prevalence of lipid profile and blood pressure among normal, prediabetic, and diabetic groups stratified by different regions is presented in Table 3.

Correlation of lipid profile and lipid ratio with HbA1c

Spearman correlation was used to determine the correlation of age, lipid profile, and lipid ratio to HbA1c, SBP, and DBP in the study population from the Asir and Jeddah region. A significant

Table 4. Spearman correlation between age, lipid profile, and lipid ratiowith HBA1c level.

Variable		HbA1C		SBP		DBP	
		Asir	Jeddah	Asir	Jeddah	Asir	Jeddah
Age	r	0.216	0.352	0.088	0.431	0.510	0.147
	p	0.000	0.000	0.000	0.000	0.004	0.000
TC	r	0.271	0.313	0.055	0.053	0.136	0.123
	p	0.002	0.004	0.002	0.001	0.000	0.000
LDL	r	0.213	0.471	0.062	0.023	0.133	0.097
	p	0.009	0.001	0.001	0.004	0.000	0.000
Triglycerides	r	0.325	0.236	0.177	0.155	0.187	0.170
	p	0.000	0.000	0.000	0.000	0.000	0.000
HDL	r	-0.172	-0.156	-0.080	-0.062	-0.073	-0.070
	p	0.000	0.000	0.000	0.000	0.000	0.000
TC/HDL	r	0.121	0.150	0.108	0.090	0.162	0.153
	p	0.000	0.000	0.000	0.000	0.000	0.000
LDL/HDL	r	0.169	0.591	0.100	0.053	0.151	0.123
	p	0.000	0.000	0.000	0.001	0.000	0.000

positive correlation was observed between age, TC, LDL TG, TC/HDL ratio, LDL/HDL ratio with HbA1c in both areas (Table 4). This finding demonstrates that the increase in the value of age, lipid profile, and lipid ratio will tend to experience an increase in HbA1c value. However, a significant negative correlation (inverse correlation) was observed between HDL with HbA1c levels in both regions. This finding illustrates that an increase in HDL's value will tend to experience a decrease in HbA1c value.

Risk analysis model of lipid profile and lipid ratio

Prediction models were performed by ROC analysis on lipid ratio parameters to risk of diabetes as the outcome of our study (Figure 1). TC/HDL ratio, LDL/HDL ratio, and triglycerides may be used as a predictive model but they are with the area under the curve (AUC) > 0.5 (Table 5). In the Asir region, TC/HDL ratio parameters have a sensitivity value of 68% and specificity of 59.9% with a cut-off value of 3.16, LDL/HDL parameter has a sensitivity of 52.1%, and specificity of 49.6% with a cut-off value of 2.31. At the same time, TG parameters have a sensitivity of 72.4% and specificity of 52.7%, with a cut-off value of 89.5. In the Jeddah region, TC/HDL ratio parameters have a sensitivity value of 73.2% and specificity of 66.5%, with a cut-off value of 3.95. LDL/HDL parameter has a sensitivity of 70.3%% and specificity of 66.5%, with a cut-off value of 2.43. In comparison, TG parameters have a sensitivity of 79.2% and specificity of 56.5%, with a cut-off value of 99.5.

Adjusting for age, logistic regression analysis as indicated in Table 6 demonstrates the risk of prediabetes (OR=1.205, $p < 0.05$)) and diabetes (OR=1.93, $p < 0.05$) is significantly higher in Jeddah region. Prediabetes and diabetes showed a significant association ($p < 0.05$) with high TC (OR =1.424 and 1.236) and borderline high TC (OR = 1.231 and 1.128), very high LDL (OR = 0.819 and 1.384) low HDL (OR = 1.43 and 1.334), high TG (OR = 1.398 and 2.305) and borderline high TG (OR 1.297 and 2.352), high TC/HDL (OR = 0.991 and 1.105) and high LDL/HDL ratio (OR= 1.040 and 0.784) respectively.

DISCUSSION

The different clinical and epidemiological investigation has reported the significantly high prevalence (18.3%) of diabetes in Saudi Arabia (Basulaiman et al., 2014; Al-Kaabba et al., 2012; Al-Hassan et al., 2018; Al Amri et al., 2019; Enani et al., 2020; Alzahrani et al., 2019). As far as we know, this is one of the first studies in Saudi Arabia to examine the impact of geographic/ environmental factors on lipid profiles and their relationship with glycated hemoglobin levels and blood pressure in study populations from two different locations in Saudi Arabia. The present study focused on the association between HbA1c and lipid profile among the Saudi population from two different geographical locations.

Unidentified dyslipidemia frequently accompanies diabetes. As discussed earlier, dyslipidemia is characterized by an abnormal rise in lipid profile (TC,

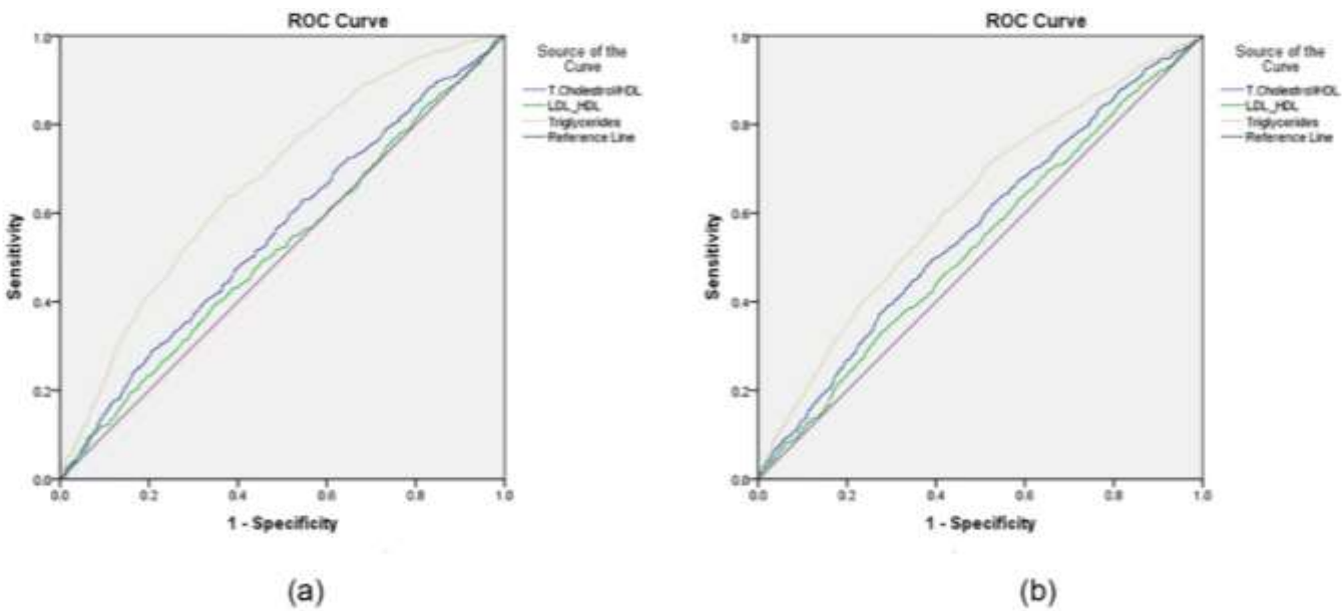

Figure 1. ROC analysis of lipid profile and lipid ratio as a predictive risk of diabetes in (a) Asir region and (b) Jeddah region.

Table 5. Area under the curve (AUC), cut-off value, sensitivity, specificity of lipid ratio, and lipid profile.

Parameter	AUC	*p*	Cut off value	95% CI	Sensitivity (%)	Specificity (%)
Asir						
TC/HDL	0.554	0.000	3.16	0.53-0.58	68	59.9
LDL/HDL	0.517	0.145	2.31	0.49-0.54	52.1	49.6
TG	0.673	.000	89.5	0.65-0.67	72.4	52.7
Jeddah						
TC/HDL	0.563	0.000	3.95	0.54-0.58	73.2	66.5
LDL/HDL	0.529	0.009	2.43	0.50-0.55	70.3	66.5
TG	0.622	0.000	99.50	0.60-0.64	79.2	56.5

LDL, and TG) beyond the normal value (Artha et al., 2019). In our study, a significantly higher prevalence of dyslipidemia in the prediabetes and diabetes group was observed from both the region. This is in agreement with other studies conducted by Khan et al. in Riyadh (Ahmad, 2007). Investigation of lipid parameters among diabetic patients showed that lipid parameter was significantly higher in patients with non-glycemic control (HbA1c > 7) compared to reasonable glycemic control (HbA1c ≤ 7). Another study was conducted in 2019 to evaluate the association of lipid profile and HbA1c in Indonesia. They reported a significantly higher lipid and lipid ratio profile and lower HDL in the group with poor glycemic control (Artha et al., 2019). Similarly, Enani et al. reported that the prevalence of dyslipidemia in Saudi adults was 62% (Enani et al. 2020). Many other studies indicated that dyslipidemia is significantly associated with increased risk of prediabetes and diabetes and the rapid onset and advanced stage of diabetic vascular complications (Bhowmik et al., 2018; Zheng et al., 2017; Alzahrani et al., 2019). In our study, a significantly high association of prediabetes and diabetes with lipid profile (TC, LDL, and TG) and lipid ratio (TC/HDL and LDL/HDL) was noted in regression analysis, similar to other investigations (Chakarova et al., 2009; Chang and Wu, 2013; Owei et al., 2016; Alzahrani et al., 2019).

We observed a significantly high prevalence of prediabetes and diabetes (Table 3) among dyslipidemia groups living permanently in Jeddah compared with their counterparts in the Asir region. This difference could be due to various factors, including environmental, genetic, and lifestyle. Our result is consistent with the recent investigation carried out to determine the association of prediabetes with lipid profile in Jeddah (Al Amri et al., 2019). They reported a significantly high prevalence of prediabetes (28.7%) and dyslipidemia (54%) in the study subject (n=613) (Al Amri et al., 2019). Another study was conducted in 2016 to investigate the congruent

Table 6. Odds ratio (OR) with 95%CI of different lipid parameters for having the risk of prediabetes and diabetes.

	Prediabetes				Diabetes			
	p	**OR (95%CI**	**95% CI of OR**		**Sig.**	**OR (95% CI**	**95% CI of OR**	
			Lower	**Upper**			**Lower**	**Upper**
Low altitude	0.002	1.205	1.068	1.359	0.036	1.93	0.807	2.055
Male	0.000	1.255	1.119	1.407	0.242	1.08	0.949	1.228
TC								
High	0.035	1.424	1.025	1.976	0.270	1.236	0.849	1.800
Borderline high	0.030	1.231	1.021	1.485	0.277	1.128	0.907	1.403
LDL								
Very high	0.399	0.819	0.515	1.303	0.001	0.384	0.224	0.660
High	0.146	0.783	0.564	1.088	0.000	0.455	0.313	0.661
Border line high	0.163	0.852	0.681	1.067	0.000	0.552	0.430	0.708
HDL								
At risk	0.007	1.430	1.104	1.853	0.000	1.788	1.334	2.396
Triglycerides								
Very high	0.083	0.312	0.83	1.166	.036	2.425	1.062	5.540
High	0.003	1.398	1.124	1.738	0.000	2.306	1.842	2.887
Borderline high	0.004	1.297	1.084	1.551	0.000	2.352	1.958	2.824
TC/HDL ratio								
High	0.991	1.001	0.783	1.281	0.461	1.105	0.848	1.438
LDD/HDL ratio								
High	0.760	1.040	0.808	1.339	0.829	1.031	0.784	1.355

association of lipid profile with glycemic control in the USA (Owei et al. 2016). They reported that a higher level of TC, LDL, and TG significantly increased the risk of prediabetes/diabetes (Owei et al., 2016). Our finding of a statistically significant relationship between plasma lipids and the likelihood of developing prediabetes or diabetes at lowland is consistent with previous experimental and clinical findings (Lee et al., 1994; Tirosh et al., 2008; Liao et al., 2015; Aryal et al., 2017; Enani et al., 2020; Woolcott et al., 2014; Woolcott et al., 2016; Bahijri et al., 2016).

In two different studies Sharma (Sharma 1990) and Dominguez et al. (Domínguez et al., 2000) investigated the association of lipid profile with altitude from an epidemiological point of view; they reported that level of HDL increases, whereas LDL decreases with altitude (Domínguez et al., 2000; Sharma 1990). Similarly, in a survey study, the population living in a hilly neighborhood may be protective from diabetes (Villanueva et al., 2013). These findings indicated the influence of altitude on lipid profile and HbA1c. In concomitant with the above studies and results obtained from our study, our study revealed that the population living in the Jeddah region has a higher risk of prediabetes (OR =1.205) and diabetes (OR=1.93) compared to the population living in the Asir region. Furthermore, our result of the high prevalence of prediabetes and diabetes in Jeddah (lowland) is supported by the fact that population residents at high altitudes, compared with the population at lowlands, have lower glycemia (Castillo et al., 2007; Garmendia et al., 1972).

Similarly, a lower risk of diabetes has been reported for pregnant and nonpregnant females residing at highlands (Krampl et al., 2001; Zamudio et al., 2010; Picon 1963). Besides, residents at high altitudes have better glucose tolerance (Picon, 1963; Calderon and Llerena, 1965). A possible reason to explain the inverse relation between altitude and risk of diabetes or prediabetes is the low basal metabolic rate of the people living at low altitudes compared to those who lived at high altitudes (Kashiwazaki et al., 1995). Also, there is an inverse relation between highland and ambient temperature (Montgomery, 2006; Woolcott et al., 2014; Woolcott et al., 2016). Therefore, the highlanders can reasonably be expected to have increased cold-induced thermogenesis decreased appetite at high altitudes (Palmer and Clegg, 2014; Woolcott et al., 2014; Woolcott et al., 2016).

Furthermore, people who live in high altitude and hilly areas may be subjected to more walking and physiologically strenuous physical activity, contributing to increased calorie consumption, providing a protective barrier against weight gain, and reducing the risk of prediabetes and diabetes. Obesity has been identified as a significant contributor to diabetes-related insulin resistance and hyperglycemia (Wellen and Hotamisligil, 2005; Martyn et al., 2008). The malfunction of energy homeostasis can cause obesity due to genetic predisposition (Martyn et al., 2008). However, recent research demonstrated that obesity may not always be linked to hereditary problems. It may be related to theinability of the human body to manage high-energy food. In addition, deskbound lifestyle and lack of physical activity play a significant effect in the development of obesity (Hossain et al., 2007; Wild et al., 2004; Rocchini 2002).

Furthermore, apoptosis (cell death) of adipocytes linked with obesity appears to be the critical factor responsible for insulin insensitivity (Martyn et al., 2008). By releasing free fatty acids, adipocytes inhibit glucose absorption in peripheral organs (Martyn et al., 2008). Other etiological factors associated with obesity-induced insulin resistance pathogenesis include oxidative stress, mitochondrial dysfunction, intracellular lipid accumulation in skeletal muscle and liver, and decreased β-oxidation (Martyn et al., 2008). By selecting study participants from Saudi Arabia, we could limit the impact of racial, cultural, and dietary characteristics because they share almost the same ethnic and cultural background and nutritional habits. Thus, the main factors between the population appear to be geographical/environmental.

When we compared the overall blood pressure of study subjects from two different geographical locations, we observed small but statistically significant high SBP and DBP in the study population from the Asir region compared to those from the Jeddah region. Also, the SBP and DBP of prediabetes and diabetes groups from the Asir region were significantly higher than the same group in the Jeddah region. This interpopulation variation in BP has been well documented in the literature (Duh and Willingham, 1986; Sever et al., 1980; Sever et al., 1979). It could be well explained by racial, cultural, dietary, or environmental factors (Duh and Willingham, 1986; Sever et al., 1980; Sever et al., 1979). Our results are consistent with the previous studies, which reported the increased BP at high altitudes (Khalid et al., 1994; Khalid and Adzaku, 1995). An investigation conducted by Khalid et al. (Khalid et al. 1994; Khalid and Adzaku, 1995) reported a significantly higher risk of developing hypertension in the population living at a higher altitude than those living at sea level. Recently Hirschler et al. demonstrated that as the altitude increases, BP levels rises significantly in indigenous population from similar backgrounds living permanently at different altitudes (Hirschler et al., 2019). In view of the positive correlation of blood pressure (SBP, DBP) with age, and lipid profile (TC, LDL, TG) and lipid ratio (TC/HDL, LDL/HDL ratio) in both regions, we suggest that difference in BP (SBP and DSP) between Asir and Jeddah region may be due, in part, to a more significant effect of altitude on increase blood viscosity and cardiac output (Ahmed et al. 2016; Puri et al. 1986). Lower oxygen tension, lower humidity, higher radiation, lower temperature, and lower barometric pressure are some of the atmospheric changes that occur as altitude increases, leading to increased blood pressure (CedarsSinai, 2021).

Our study has some points of limitation as well as strength. The main strength of this study is that it is the first kind of comparative study in Saudi Arabia using a different definition of lipid profile and commonly used components for the definition of prediabetes and diabetes. Furthermore, we had an almost complete set of biochemical data required for our study, and we were able to compute comparative analysis, correlation, and logistic regression. The main limitation is that body weight, and BMI was not available for the study subject.

Conclusions

This is the first retrospective cross-sectional study investigating the geographical/environmental effects on lipid profile and its association with HbA1c and BP in the Saudi population. Lipid profile and lipid ratio (TC/HDL and LDL/HDL) appear to be the potential markers that can be used to predict prediabetes/diabetes in the general population. A higher value of lipid profile (TC, LDL, and TG) and lower value of HDL are prevalent in the population with poor or non-glycemic control (HbA1c <7). The study finding demonstrates that the increase in the value of age, lipid profile, and lipid ratio will tend to experience an increase in HbA1c value. The laboratory assessment demonstrated a good correlation between the prevalence of dyslipidemia and HbA1c in both regions. A higher prevalence of prediabetes and diabetes was found in Jeddah (lowland area) of Saudi Arabia. The current study demonstrates the inverse association between diabetes and lipid profile with highland. However, a positive effect of highland on blood pressure was also observed.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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