EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

PHYSIOLOGY & MOLECULARBIOLOGY

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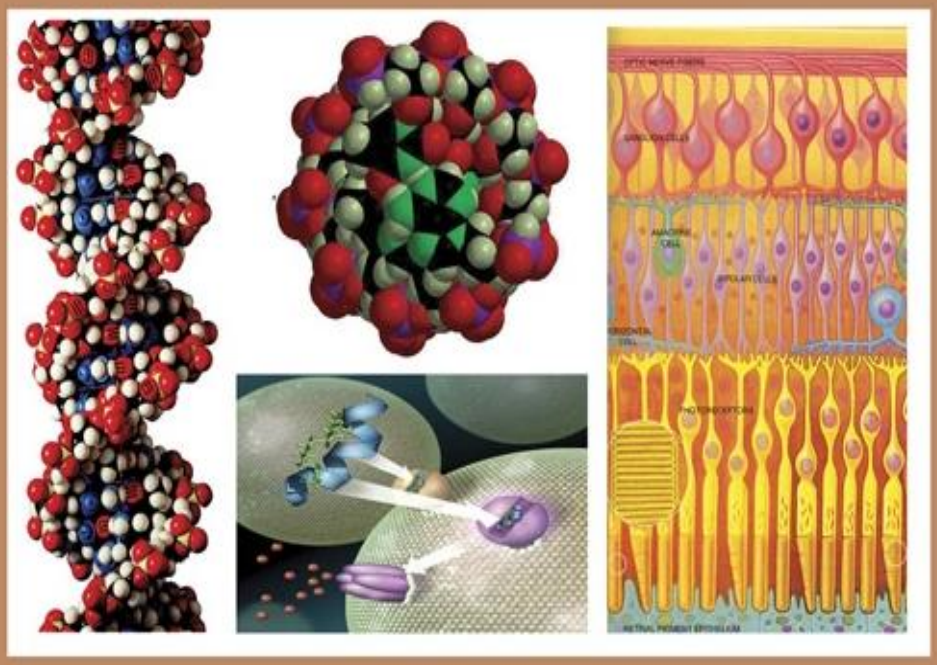

ISSN
2090-0767

WWW.EAJBS.EG.NET

Vol. 14 No. 1 (2022)

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Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 14(1) pp21-30 (2022)*
DOI: 10.21608/EAJBSC.2022.213921

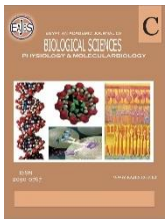
Egypt. Acad. J. Biolog. Sci., 14(1):21-30 (2022)

Egyptian Academic Journal of Biological Sciences

C. Physiology & Molecular Biology

ISSN 2090-0767

www.eajbsc.journals.ekb.eg



Association between Lipid Levels and Short-Term Heart Rate Variability (HRV) In Type 2 Diabetes

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ARTICLE INFO

Article History

Received:26/11/2021

Accepted:12/1/2022

Available:13/1/2022

Keywords:

HRV, lipids, total cholesterol, LDL, triglycerides

ABSTRACT

Background: There are plenty of studies available to demonstrate the effect of diabetes on short-term Heart Rate Variability (HRV) but not enough about lipids, especially in our region. Hence, we aimed to study the influence of total cholesterol and individual lipid fractions on short-term HRV in type 2 diabetics.

Methods: As per the set criteria, 70 newly diagnosed type 2 diabetics were recruited and grouped based on their cholesterol levels. Both the time domain and the frequency domain measures of short-term HRV were acquired and subjected to statistical analysis. This was a cross-sectional observational study.

Results: Elevated total cholesterol group showed a reduction in Standard deviation of all NN intervals (SDNN) and High Frequency (HF) power and an increase in Low-Frequency power / High-Frequency power (LF/HF) ratio in comparative analysis. Similarly, the high low-density lipoproteins (LDL) group showed a decrease in square root of the mean of the sum of the squares of the differences between adjacent NN intervals (SDNN) and RMSSD but a rise in LF/HF ratio. Moreover, total cholesterol is negatively correlated with SDNN, RMSSD, and HF power while total cholesterol and LDL are positively correlated with LF/HF ratio. Total cholesterol, LDL, and triglycerides had an independent association with HF.

Conclusions: Our study shows higher levels of total cholesterol, LDL and triglycerides decrease cardiovagal activity. Hence, based on this we conclude abnormal lipid levels depress HRV.

INTRODUCTION

Heart Rate Variability (HRV) assesses the integrity of the autonomic nervous system as it is influenced by the changes in the sympathetic as well as the vagal activity (Electrophysiology, 1996). Altered HRV may be a sign of disease or a risk factor for impending cardiac disease (Christensen *et al.,* 1999).

Time-domain analysis of HRV is based on the heart rate and the changes in the time interval between two successive normal to normal complexes. It quantifies the amount of HRV observed during the monitoring period. The time-domain measures considered in this study are Standard Deviation of all NN intervals (SDNN), Square Root of the Mean of the Sum of the Squares of the Differences between adjacent NN intervals (RMSSD), and the number of pairs of adjacent NN intervals differing more than 50 milliseconds in the entire recording divided by the total number of NN intervals (pNN50). Of these three, SDNN is a measure of total variability while RMSSD and pNN50 estimate high-frequency variations in heart rate (Electrophysiology, 1996).

Frequency domain analysis decomposes the series of sequential RR intervals into a sum of sinusoidal functions of different amplitudes and frequencies. The measures considered here are high frequency (HF) and low frequency (LF) components which calculate the absolute or relative amount of signal energy within the component bands with each frequency band denoting its significance (Electrophysiology, 1996). HF reflects cardiovagal activity while LF represents the cardiac sympathetic drive (Shaffer & Ginsberg, 2017).

Presently, the burden of the non-communicable disease diabetes on our society is huge. Type 2 diabetes mellitus is highly prevalent among older individuals and the diabetes risk is increasing alarmingly among younger individuals too, especially when they have a family history coupled with a sedentary lifestyle (Subramani *et al.,* 2019).

Similarly, the prevalence of dyslipidemia in the Indian population is very high and it has been established that diabetes and dyslipidemia are closely associated with major cardiovascular risk factors (Joshi *et al.*, 2014).

Diabetes mellitus tends to affect HRV, and a reduction in time domain measures is associated with autonomic neuropathy even before its clinical manifestation (Electrophysiology, 1996). Even in the early stages of diabetes, the resulting metabolic impairment is associated with cardiac autonomic impairment and it worsens progressively as the disease progresses (Schroeder *et al.*, 2005). Moreover, regardless of their cardiac status, diabetic patients have a decreased HRV due to cardiac autonomic neuropathy when compared to the general population (Singh *et al.,* 2000).

Similarly, dyslipidemia also was thought to play a role in the development of autonomic dysfunction. However, its role was not clear due to conflicting results from the available studies about the effect of individual lipid fractions (Chaudhuri *et al.,* 2012) (Kundu *et al.,* 2013) (Danev *et al.,* 1997). Even the few available studies are not reflective of our population.

Since dyslipidemia is usually associated with type 2 diabetes mellitus, for our study, we used a study population consisting of diabetics. Through appropriate study design and analytical methods, we arrived at the influence of total and individual lipid fractions on short-term HRV.

MATERIALS AND METHODS

This is a cross-sectional observational study approved by the Institutional Human Ethics Committee (Project No. 19/063). The study was conducted in the outpatient department of PSG Hospitals, PSG Institute of Medical Sciences & Research where strict adherence to principles was taken care of. Informed consent was obtained from the participants and complete patient confidentiality was ensured. The study participants were selected from newly diagnosed type 2 diabetic patients. Diabetes was diagnosed based on the standard guidelines (Classification and Diagnosis of Diabetes: Standards of

Medical Care in Diabetes—2019, 2018). Both men and women of age group 35-60 with HbA1c levels between 6.5 to 7.5 were shortlisted. Among them, hypertensives, asthmatics, cardiac patients, individuals with a family history of cardiac disease, patients with thyroid disorders, pregnant individuals, and patients on HRV altering medications were excluded.

Based on the above criteria, a total of 70 people were recruited. The sample size was determined after calculation using 'r' value from a previous correlation study (Kepez et al., 2015). The 70 participants were selected in such a way that 35 people were having normal total cholesterol levels and the remaining 35 were with higher total cholesterol levels. Lipid cut-off levels were set based on the desirable lipid target levels in diabetes (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001).

The study participants were subjected to short-term HRV analysis. This involved a recording of an electrocardiogram (ECG) in Lead II for 320 seconds in a computerized student's physiograph, three-channel (INCO, Chennai). Both the time domain and frequency domain measures were acquired from the study participants using NIVIQURE-HRV software (Niviqure Meditech Private Limited, Bangalore).

Statistical Analyses:

The data obtained were statistically analyzed using SPSS software version 24. In addition to the levels of total cholesterol, the study participants were grouped based on the cut-off levels for other lipid fractions and their data also were compared accordingly. Moreover, individual lipid fractions were correlated with individual HRV measures. For statistical analysis, independent sample t-test, Pearson's correlation, and Regression analysis were employed.

RESULTS

In type 2 diabetics, when the normal total cholesterol group is compared with the high total cholesterol group (Table 1), SDNN (p= 0.036) and HF power (*p*= 0.040) showed a statistically significant reduction. However, there was a statistically significant increase in the LF/HF ratio (*p*= 0.022) (Table 1).

In type 2 diabetics with high LDL levels, SDNN (*p*= 0.009) and RMSSD (*p*= 0.011) were significantly reduced when compared to patients with a normal LDL level (Table 2). However, LF/HF ratio showed a statistically significant increase (*p*= 0.045) (Table 2).

There are no statistically significant changes in HRV parameters due to variations in the levels of triglycerides (Table 3).

In the correlation analysis (Table 4), SDNN, RMSSD and, HF power showed a statistically significant negative correlation with total cholesterol (Fig. 1A, 1B& 1C), whereas LF/HF ratio shows a statistically significant positive correlation (Fig. 1D). LF/HF ratio also has a significant positive correlation with LDL (Fig. 2). Regression analysis reveals that total cholesterol is independently in association with HF power. This is statistically significant for total cholesterol (*p*=0.002) after adjustment for age, Body Mass Index (BMI), and other lipid parameters. Regression analysis further revealed that LDL has an independent association with HF power. This is statistically significant for LDL (*p*= 0.005) after adjustment for age, BMI, and other lipid parameters. Regression analysis also reveals that triglycerides have an independent association with HF power. This is statistically significant for Triglycerides (*p*= 0.015) after adjustment for age, BMI, and other lipid parameters.

Table 1 - Comparison of HRV parameters between high and normal cholesterol levels

Variables	Groups	N	TCL (mg/dL)	Mean ± SD	p-Value
SDNN	1	35	>200	56.42 ± 8.09	0.036*
	2	35	<200	65.09 ± 25.57	
RMSSD	1	35	>200	20.24 ± 7.47	0.053
	2	35	<200	30.79 ± 30.86	
pNN50	1	35	>200	3.49 ± 3.72	0.292
	2	35	<200	5.11 ± 8.21	
HF	1	35	>200	101.59 ± 46.55	0.040*
	2	35	<200	148.86 ± 125.27	
LF	1	35	>200	75.57 ± 35.37	0.314
	2	35	<200	65.56 ± 46.38	
LF/HF	1	35	>200	0.92 ± 0.58	0.022*
	2	35	<200	0.63 ± 0.46	

*p < 0.05
TCL – Total Cholesterol
N – Number of study participants

Table 2 - Comparison of HRV parameters between high and normal LDL levels

Variables	Groups	N	LDL (mg/dL)	Mean ± SD	p-Value
SDNN	1	42	>130	56.36 ± 8.47	0.009**
	2	28	<130	67.34 ± 24.27	
RMSSD	1	42	>130	19.88 ± 7.55	0.011*
	2	28	<130	33.98 ± 33.64	
pNN50	1	42	>130	3.15 ± 3.61	0.064
	2	28	<130	6.03 ± 8.89	
HF	1	42	>130	112.16 ± 70.71	0.168
	2	28	<130	144.84 ± 125.22	
LF	1	42	>130	76.56 ± 35.79	0.138
	2	28	<130	61.58 ± 47.59	
LF/HF	1	42	>130	0.88 ± 0.57	0.045*
	2	28	<130	0.61 ± 0.46	

*p < 0.05
**p < 0.01
LDL – Low Density Lipoproteins
N – Number of study participants

Table 3 - Comparison of HRV parameters between high and normal Triglyceride levels

Variables	Groups	N	TGL (mg/dL)	Mean ± SD	p-Value
SDNN	1	37	>150	62.16 ± 21.04	0.479
	2	33	<150	59.18 ± 12.22	
RMSSD	1	37	>150	28.41 ± 29.83	0.267
	2	33	<150	22.27 ± 10.51	
pNN50	1	37	>150	5.13 ± 7.91	0.252
	2	33	<150	3.37 ± 3.96	
HF	1	37	>150	125.77 ± 113.11	0.961
	2	33	<150	124.62 ± 76.17	
LF	1	37	>150	68.33 ± 47.18	0.634
	2	33	<150	73.08 ± 33.96	
LF/HF	1	37	>150	0.81 ± 0.58	0.639
	2	33	<150	0.74 ± 0.49	

TGL – Triglycerides
N – Number of study participants

Table 4 - Correlation of HRV parameters with lipid fractions

	Value	TCL	TGL	HDL	LDL
SDNN	r	-0.237#	-0.041	-0.077	-0.213
	p	0.049*	0.738	0.526	0.077
	N	70	70	70	70
RMSSD	r	-0.266#	-0.037	-0.093	-0.221
	p	0.026*	0.760	0.442	0.066
	N	70	70	70	70
pNN50	r	-0.184	-0.029	-0.073	-0.149
	p	0.127	0.814	0.551	0.218
	N	70	70	70	70
HF	r	-0.277#	-0.062	-0.028	-0.219
	p	0.020*	0.610	0.820	0.069
	N	70	70	70	70
LF	r	0.106	-0.055	0.128	0.107
	p	0.381	0.651	0.291	0.379
	N	70	70	70	70
LF/HF	r	0.273#	0.072	0.022	0.245#
	p	0.022*	0.555	0.855	0.041*
	N	70	70	70	70

*p < 0.05
r – Correlation coefficient
N – Number of study participants
TCL – Total Cholesterol
TGL – Triglycerides
LDL – Low-Density Lipoproteins
HDL – High-Density Lipoproteins

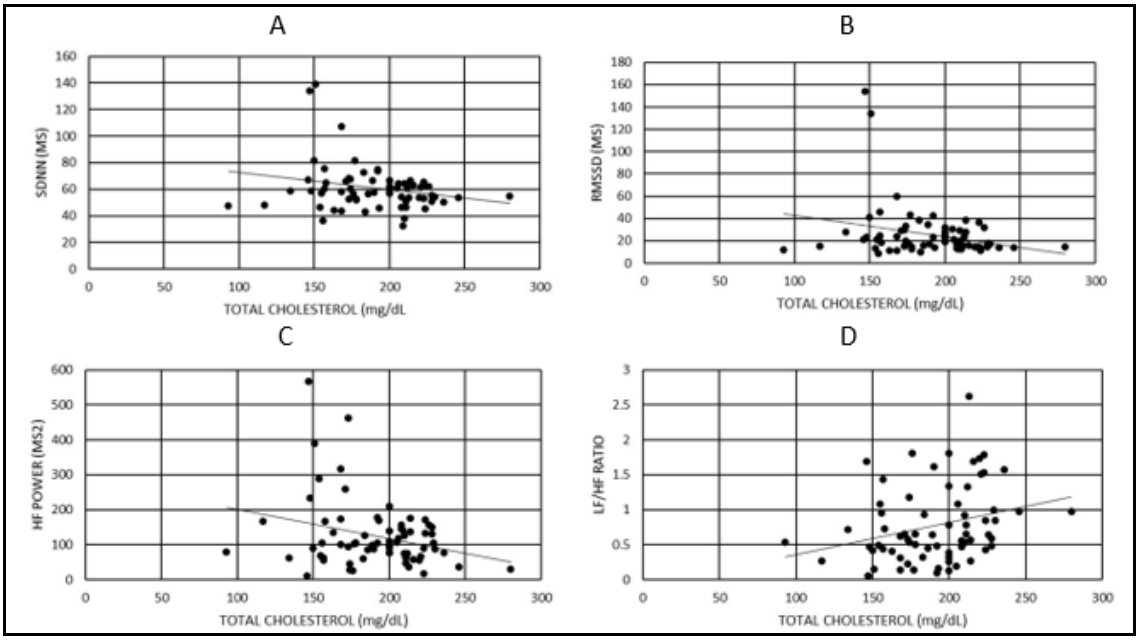

Fig. 1: Effects of Total Cholesterol on HRV
(A) Correlation of SDNN with total cholesterol
(B) Correlation of RMSSD with total cholesterol
(C) Correlation of HF power with total cholesterol
(D) Correlation of LF/HF ratio with total cholesterol.
(ms - millisecond, ms2 - millisecond2, mg/dL – milligrams per decilitre)

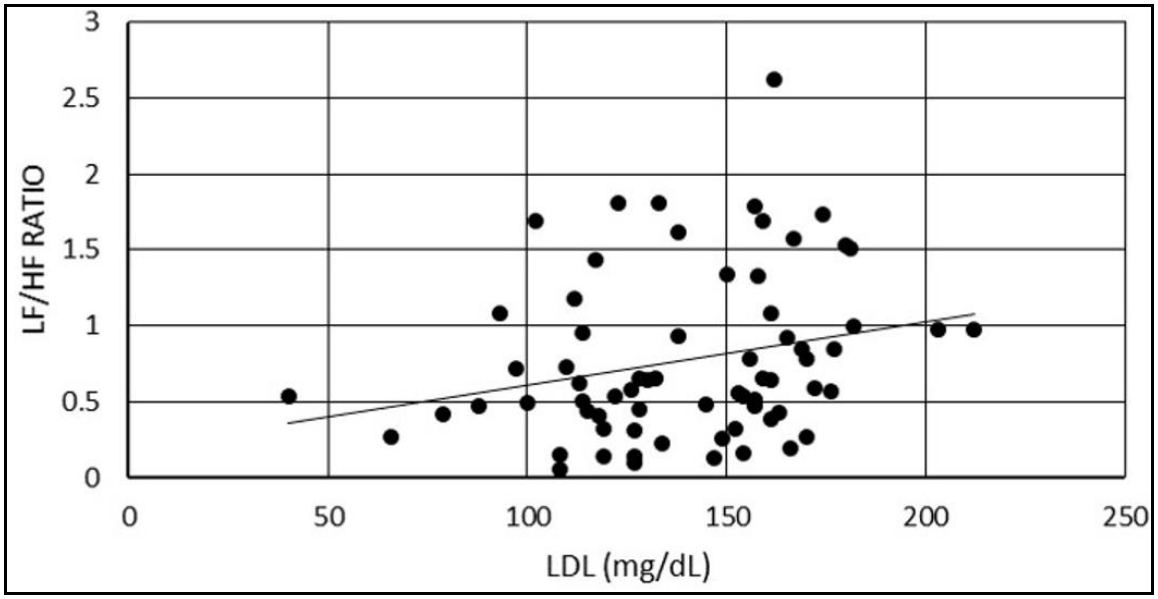

Fig. 2: Effect of LDL on HRV
Correlation of LF/HF ratio with LDL
(mg/dL – milligrams per decilitre)

DISCUSSION

A decreased HRV indicates an increased cardiovascular risk even in healthy individuals (Hillebrand *et al.,* 2013). Diabetics have been known to have a decreased HRV, predisposing them to increased cardiovascular risk due to a significantly lower vagal activity (Liao *et al.,* 1995). Some studies show elevated levels of total cholesterol and LDL in

diabetics can affect HRV adversely (Kundu *et al.,* 2013) (Burger *et al.,* 1998).

In a past study, it has been shown that in dyslipidemia, the time domain measures such as SDNN and RMSSD were significantly decreased as did the frequency domain measure HF. Moreover, LF and LF/HF ratios were significantly elevated. LF-HF ratio was found to have a positive correlation with total cholesterol and LDL cholesterol (Ali *et al.,* 2016).

Here, in our study, diabetic patients with high total cholesterol have a significantly reduced SDNN and thus show a reduction in total HRV which depicts an increased cardiovascular risk. Reduced HF power indicates compromised vagal activity. An increased LF/HF ratio may either be due to a reduction in vagal activity or an increase in the sympathetic activity or both, pointing towards an altered sympathovagal balance. These findings concur with the previous ones (Ali *et al.,* 2016).

Also, in our study, total cholesterol is negatively correlated with SDNN, RMSSD, and HF power while total cholesterol and LDL are positively correlated with LF/HF ratio. This denotes that both total HRV and vagal activity have an inverse relationship with total cholesterol. It is also evident that the sympathovagal balance is altered incrementally with increasing levels of total cholesterol and LDL. These findings of positive correlation of total cholesterol and LDL with LF/HF ratio concur with a previous study (Ali *et al.,* 2016)**.**

In another past study, it has been observed that hypertriglyceridemia was associated with reduced SDNN (Jung *et al.,* 2021). It also has been observed, that having high levels of total cholesterol, triglycerides, and LDL cholesterol as influenced by their dietary habits decreased their HF power and hence their cardiac vagal activity (Fu *et al.,* 2006).

In our study, we observed that in diabetics with high LDL levels, SDNN and RMSSD were significantly reduced, inferring that high LDL levels reduce total HRV and vagal activity. Additionally, in these individuals, LF/HF ratio was found to be elevated indicating an altered sympathovagal balance. These findings corroborate the findings of the previous study (Fu *et al.,* 2006) in showing the negative effects of high LDL cholesterol on vagal activity and sympathovagal balance.

However, we noticed that diabetics with high triglyceride levels showed no statistically significant changes in HRV parameters, which suggested that the triglyceride levels may not influence the autonomic balance. However, this needs further validation by an assessment with a larger sample in our region, as this is in contradiction with previously conducted studies (Jung *et al.,* 2021) (Fu *et al.,* 2006).

Previously, it was found that individuals with higher total cholesterol, LDL cholesterol, and triglyceride levels were having significantly reduced RMSSD and HF power. Also, they had a significantly elevated LF power and LF/HF ratio. Triglycerides were found to be independently associated with RMSSD, pNN50, and LF/HF ratio (Kepez *et al.,* 2015). Another one showed that while triglycerides had no association with any HRV measures, LDL cholesterol in men had an independent and negative association with both RMSSD and HF power (Kupari *et al.,* 1993).

Here, in our study, regression analysis revealed that LDL had an independent effect on HF power which concurs with the previous finding (Kupari *et al.,* 1993). Hence, it may be postulated that high LDL levels by having a deleterious effect on vagal activity alter the sympathovagal balance.

Our finding of Triglycerides having an independent association with HF power contradicts the findings of a past study (Kupari *et al.,* 1993). However, yet another study showing the high triglyceride levels having a sympathetic overdrive and altered sympathovagal balance indirectly supports our finding (Kepez *et al.,* 2015). Hence our finding regarding the role of Triglycerides may require further validation with a larger population sample.

In an animal study (Wang *et al.,* 2010), it has been demonstrated that hyperlipidemia is more than likely to dysregulate inflammatory cytokines while reducing cholinesterase-positive nerves and the expression of M2 receptors. This provides scientific corroboration to our findings that higher total cholesterol, LDL cholesterol, and triglyceride levels can negatively affect the vagal response.

The cumulative effect of diabetes and dyslipidemia on HRV, which was not covered under the scope of this study, can be explored further in future studies. As our findings reveal the negative effect of altered lipid levels on HRV, we stress the importance of screening for dyslipidemia in individuals at diabetic risk and recommend strict lipid control, especially in diabetics to reduce cardiovascular risk.

Conclusion

Our study reveals those higher levels of total cholesterol, LDL cholesterol, and triglycerides depress HRV by reducing vagal activity and thereby altering the sympathovagal balance. Hence, based on our findings we conclude that dyslipidemia has a deleterious effect on HRV. However, an elaborate study involving non-diabetics with altered lipid levels might be needed to have a more conclusive say on the effect of lipids on HRV. As it is non-invasive and inexpensive, HRV can be utilized as a simple tool for diagnostic and prognostic purposes in dyslipidemia apart from diabetes.

Financial Support and Sponsorship:

Indian Council of Medical Research, Short Term Studentship (STS) 2019
(Ref. No.2019/02917).

REFERENCES

Ali, T., Hussein, Y., &Elaskary, A. (2016). Heart rate variability in nondiabetic dyslipidemic young Saudi adult offspring of type 2 diabetic patients. *National Journal of Physiology, Pharmacy and Pharmacology*, 6(3), 215.

Burger, A., Hamer, A., Weinrauch, L., &D'Elia, J. (1998). Relation of Heart Rate Variability and Serum Lipoproteins in Type 1 Diabetes Mellitus and Chronic Stable Angina Pectoris. *The American Journal of Cardiology*, 81(8), 945-949.

Chaudhuri, A., Borade, N., &Hazra, S. (2012). A study of heart rate variability tests and lipid profile in postmenopausal women. *J Indian Med Assoc*, 110(4), 228.

Christensen, J., Toft, E., Christensen, M., & Schmidt, E. (1999). Heart rate variability and plasma lipids in men with and without ischaemic heart disease. *Atherosclerosis*, 145(1), 181-186.

Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2019. *Diabetes Care* 2019;42(Supplement_1):S13–S28 (2018), 42(Supplement_1), S13-S28. https://doi.org/10.2337/dc19-S002

Danev, S., Nikolova, R., Kerekovska, M., &Svetoslavov, S. (1997). Relationship between heart rate variability and hypercholesterolemia. *Central European Journal of Public Health (CEJPH)*,*5*(3), 143-6.

Electrophysiology, T. F. O. T. E. S. O. C. T. N. A. S. O. P. (1996). Heart rate variability: standards of measurement, physiological

interpretation, and clinical use. *Circulation*, 93(5), 1043-106.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. (2001). Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA: *The Journal of The American Medical Association*, 285(19), 2486-2497.

Fu, C., Yang, C., Lin, C., &Kuo, T. (2006). Effects of Long-Term Vegetarian Diets on Cardiovascular Autonomic Functions in Healthy Postmenopausal Women. *The American Journal of Cardiology*, 97(3), 380-383.

Hillebrand, S., Gast, K., de Mutsert, R., Swenne, C., Jukema, J., &Middeldorp, S. et al. (2013). Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression. *EP Europace*, 15(5), 742-749.

Joshi, S., Anjana, R., Deepa, M., Pradeepa, R., Bhansali, A., &Dhandania, V. et al. (2014). Prevalence of Dyslipidemia in Urban and Rural India: The ICMR–INDIAB Study. *Plos ONE*, 9(5), e96808.

Jung, H., Choi, Y., & Kim, S. (2021). Association between Metabolic Syndrome and Heart Rate Variability. *The Korean Journal of Obesity*, 14(4), 220-227.

Kepez, A., Dogan, Z., & Mammadov, C. (2015). Evaluation of Association Between Hyperlipidemia and Heart Rate Variability in Subjects Without Apparent Cardiovascular Disease. *Kosuyolu Heart Journal*, 18(1), 29-33.

Kundu, D., Bandyopadhyay, U., Ghosh, E., Roy, A., Mandal, T., & Ray, D. (2013). A comparative study of heart rate variability tests and lipid profile in healthy young adult males and females. *Nigerian Journal of Clinical Practice*, 16(4), 424.

Kupari, M., Virolainen, J., Koskinen, P., &Tikkanen, M. (1993). Short-term heart rate variability and factors modifying the risk of coronary artery disease in a population sample. *The American Journal of Cardiology*, 72(12), 897-903.

Liao, D., Cai, J., Brancati, F., Folsom, A., Barnes, R., Tyroler, H., &Heiss, G. (1995). Association of vagal tone with serum insulin, glucose, and diabetes mellitus — The ARIC Study. *Diabetes Research and Clinical Practice*, 30(3), 211-221.

Schroeder, E., Chambless, L., Liao, D., Prineas, R., Evans, G., Rosamond, W., &Heiss, G. (2005). Diabetes, Glucose, Insulin, and Heart Rate Variability: The Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care*, 28(3), 668-674.

Shaffer, F., & Ginsberg, J. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Frontiers in Public Health*, 5.

Singh, J., Larson, M., O'Donnell, C., Wilson, P., Tsuji, H., Lloyd-Jones, D., & Levy, D. (2000). Association of hyperglycemia with reduced heart rate variability (The Framingham Heart

Study). *The American Journal of Cardiology*, 86(3), 309-312.

Subramani, S., Yadav, D., Mishra, M., Pakkirisamy, U., Mathiyalagen, P., & Prasad, G. (2019). Prevalence of Type 2 Diabetes and Prediabetes in the Gwalior-Chambal Region of Central India. *International Journal of Environmental Research and Public Health*, 16(23), 4708.

Wang, Y., Hu, H., Wang, S., Tian, Z., Zhang, Q., & Li, Q. et al. (2009). Exercise benefits cardiovascular health in hyperlipidemia rats correlating with changes of the cardiac vagus nerve. *European Journal of Applied Physiology*, 108(3), 459-468.

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