Correlation of serum cardiolipin levels with physical activity in type 2 diabetes mellitus patients

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ABSTRACT

Cardiolipin, a critical phospholipid involved in mitochondrial function, has a potential role in the pathogenesis of type 2 diabetes mellitus. This research aims to assess serum cardiolipin levels in type 2 diabetic patients and examine their correlation with their physical activity, age, and gender. The study employed cross-sectional research conducted at Lahore Garrison University and Lahore Medical Research Center. Physical activity and serum cardiolipin levels were measured using the International Physical Activity Questionnaire (IPAQ) and a chemical analyzer, respectively. A sample size of 80 participants was analyzed statistically using *t*-tests and analysis of variance in GraphPad Prism 8.0.2 (263). IPAQ demonstrated that most patients (56%) were of the moderate activity category. Across age groups, there were significant differences in cardiolipin and blood sugar levels. Similarly, important differences were found in serum cardiolipin (p=0.0001), glycated hemoglobin (p=0.0499), and blood sugar (p=0.0021) levels among low, moderate, and vigorous physical activity groups. No significant difference was noticed among genders. Conclusions: Our research highlighted the potential age-dependent impact of physical activity on cardiolipin levels, emphasizing its relevance to mitochondrial health. A significant difference was also found between physical activity and blood sugar.

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Introduction

Inadequate insulin synthesis or utilization is compromised; the end consequence is hyperglycemia, a sign of diabetes, a chronic metabolic condition.[1] Worldwide, more than 415 million individuals are affected by diabetes, and it is determined that about 193 million have unrecognized diabetes.[2] According to research, in Pakistan, 33-36 million people have diabetes, and a large population of about 8.9 million people are undiagnosed cases within the diabetic population. Moreover, 11 million adults have impaired glucose metabolizing systems.[3] Studies have shown that cardiolipin content is reduced in the β-cells of diabetic individuals, which may result in lower insulin secretion from impairment of mitochondrial activity.[4] Type 2 diabetics and those at high risk for getting the disease have impaired mitochondrial capacity in their skeletal muscles.[5] To reduce the prevalence of diabetes in both vulnerable populations and the public, primary prevention is of paramount importance. A key component of preventing and managing type 2 diabetes mellitus (T2DM) is early diagnosis and engaging in

regular physical activity.[2] The mitochondria are the primary sites of cardiolipin presence in cells. This lipid plays a significant role in mitochondrial energy production, oxidative phosphorylation, and apoptosis.[6] Recent research has demonstrated that cardiolipin contributes significantly to the development and progression of diabetes.[7] Cardiolipin plays an important role in maintaining the integrity and performance of the mitochondrial membrane. This is particularly important in pancreatic β-cells, which rely heavily on oxidative phosphorylation for adenosine triphosphate production. Inflammation and oxidative stress can be controlled by cardiolipin, in addition to its function in mitochondria. Insulin resistance and β-cell dysfunction in diabetes are known to be exacerbated by inflammation and oxidative stress.[5]

The regulation of apoptosis has also been linked to cardiolipin (cell death). Alteration in cardiolipin composition or integrity can disrupt mitochondrial function, triggering apoptosis in β-cells.[8] Lifestyle changes, such as eating well, exercising regularly, and controlling one's weight, are the foundation for managing T2DM. Medications may also be prescribed to help control blood sugar levels. As the condition progresses, insulin therapy may become essential in some cases.[9] By knowing the significant role of cardiolipin and its association with physical activity throughout diabetes and how it affects glucose metabolism, we can improve the quality of life by decreasing the risk of several health damages. Identifying new therapies targeting cardiolipin is proposed to prevent or mitigate the development and progression of diabetes. Given the many advantages of promoting physical activity to improve diabetes-related health outcomes, there is an immediate need to do so. Overall, by conducting this research, we aim to shed light on all facets of diabetes and the importance of prevention and treatment strategies to address this growing public health concern.

Materials and Methods

A cross-sectional study was conducted at Lahore Garrison University and Lahore Medical and Research Center, Lahore, Pakistan. It was designed to evaluate serum cardiolipin levels in type 2 diabetic patients in different physical activity categories: low, medium, and high, to better manage their condition and avoid complications. A sample size of 80 participants aged between 19 and 65 was chosen. Data for physical activity were collected from the International Physical Activity Questionnaire. Tests were performed using a Rayto RT-6000 Elisa microplate reader (China). Data were analyzed statistically using *t*-tests and analysis of variance (ANOVA) in GraphPad Prism 8.0.2 (263). The following formula [Eq. 1] was used to estimate the sample size based on the prevalence of T2DM, which was 16.98% at a 95% confidence level and an 8% margin of error:

$$n = \frac{z^{2-\alpha/2}\, p(1-p)}{d^2} \quad \text{[Eq. 1]}$$

where p is the proportion of poor knowledge (0.16989), d is the marginal error set at 8%, α=0.05, Z is the standard normal deviation for a 95% confidence interval, and n is the number of respondents (85).

Statistical analysis

With the help of Graph Pad Prism, we ran the statistical tests. Mean, standard deviation, and percentages were analyzed by descriptive statistics. The pp-value was calculated using an unpaired t-test, and a significance level of less than 0.05 was used in the ordinary one-way ANOVA.

Ethical consideration

Approval for this work was granted by Lahore Garrison University's Biosafety and Research Ethics Committee (BSRE No. 022). All requirements were met in accordance with the ethical standards outlined in ORIC's current guidelines. All patients were asked to sign an informed consent form before participating in this study.

Results

Of 80 participants, 26 (32.5%) were male, and 54 (67.5%) were female, with mean ages of 49.62±13.73 and 50.22±13.02 years, respectively. The mean body weight of males and females was 73.69±27.04 and 76.37±14.00, respectively. In Table 1, p>0.05 of demographics shows that the data among genders are normally distributed.

Gender-wise comparison of serum cardiolipin, glycated hemoglobin, and blood sugar levels in patients with type 2 diabetes

Out of 80 participants 26 (32.5%) were male, and 54 (67.5%) were female. The mean level of cardiolipin in males was 0.1634±0.05958, and in females was 0.1411±0.07447. A p-value of 0.1862 indicates that cardiolipin levels across genders are normally distributed and show no significant association. The mean level of glycated hemoglobin (HbA1c) in males was 8.308±2.363, and in females, it was 7.83±1.671. A p-value of 0.3002 indicated the insignificant difference in HbA1c levels between males and females. The mean level of blood sugar fasting/random (BSF/R) in males was 164.0±50.87, and in females, it was 176.4±78. A p-value of 0.4659 indicated that the levels of BSF/R did not differ significantly between genders (Table 2).

Table 1. Demographics of participants.

Demographics	Male	Female	Total	p
Frequency (%)	26 (32.5)	54 (67.5)	80 (100.0)	—
Age (years), (mean±SD)	49.62±13.73	50.22±13.02	50.03±13.08	0.894
Body weight (kg), (mean±SD)	73.69±27.04	76.37±14.00	75.50±18.90	0.6801

SD, standard deviation.

Table 2. Gender-wise comparison of serum cardiolipin levels in people with type 2 diabetes.

Gender	Frequency (%)	Cardiolipin (mean±SD)	HBa1c (%) (mean±SD)	Blood sugar (mg/dL) (mean±SD)
Male	26 (32.5)	0.1634±0.05958	8.308±2.363	164.0±50.87
Female	54 (67.5)	0.1411±0.07447	7.83±1.671	176.4±78
Total	80 (100.0)	0.1484±0.07083	7.985±1.933	172.4±71.13
p		0.1862	0.3002	0.4659

SD, standard deviation; HBa1c, glycated hemoglobin.

Table 3. Comparison of serum cardiolipin, glycated hemoglobin and blood sugar fasting/random levels in people with type 2 diabetes with respect to age groups.

Age	Frequency (%)	Cardiolipin (mg/dL) (mean±SD)	HbA1c (%) (mean±SD)	Blood sugar (mg/dL) (mean±SD)
≤40 years	16 (20.0)	0.1485±0.0338	7.900± 1.922	182.8±54.00
41-50 years	42 (52.5)	0.1302±0.0259	8.310± 2.011	182.9±85.38
51-60 years	8 (10.0)	0.1858±0.0936	6.875± 0.7265	119.3±13.99
>60 years	14 (17.5)	0.1813±0.1373	7.743± 1.990	159.1±38.46
Total	80 (100.0)	0.1484±0.0708	7.985±1.933	172.4±71.13
p		0.0402*	0.2506	0.0961

SD, standard deviation; HBa1c, glycated hemoglobin.

Table 4. Comparison of physical activity with cardiolipin levels in people with type 2 diabetes.

Physical activity (MET min/week)	Frequency (%)	Cardiolipin (mg/dL) (mean±SD)	HbA1c (%) (mean±SD)	Blood sugar (mg/dL) (mean±SD)
Low	18 (22.5)	0.2078±0.1245	7.300±1.223	164.9±46.25
Moderate	56 (70)	0.1298±0.02695	8.046±1.932	164.6±60.10
High	6 (7.5)	0.1437±0.03132	9.467±2.792	267.3±142.2
Total	80 (100.0)	0.1484±0.07083	7.985±1.933	172.4±71.13
p		0.0001	0.0499	0.0021

MET, minutes per week quantifies exercise volume by multiplying the activity's intensity (METs) by its duration (minutes); SD, standard deviation; HBa1c, glycated hemoglobin.

Comparative of serum cardiolipin, glycated hemoglobin and blood sugar fasting/random levels in people with type 2 diabetes across age groups

Table 3 illustrates the age-wise comparison of serum cardiolipin, HbA1c, and BSR/F levels in patients with T2DM. Mean of serum cardiolipin levels in different age groups with their respective mean age ≤40 years (0.1485±0.03382), 41-50 years (0.1302±0.02598), 51-60 years (0.1858±0.09362) and >60 years (0.1813±0.1373). The p-value (0.0402) indicates a significant difference in cardiolipin levels across age groups, suggesting that this substance varies significantly with age in T2DM patients. Regarding HbA1c and BSR/F, their respective *p*-values of 0.2506 and 0.0961 indicate that age does not significantly affect HbA1c or BSR/F in T2DM patients (Table 3).

Comparison of physical activity with cardiolipin levels in people with type 2 diabetes

Serum cardiolipin, HbA1c, and BSR/F levels were compared to the physical activity of T2DM patients, divided into three groups: low, moderate, and high levels of physical exercise. The mean value of cardiolipin in the low physical activity group was 0.2078±0.1245 mg/dL. The mild and high physical activity groups were 0.1298±0.02695 mg/dL and 0.1437±0.03132 mg/dL, respectively. The p-value of 0.0001 indicates a highly significant association between cardiolipin levels and physical activity in T2DM patients, and that T2DM patients with high physical activity had lower cardiolipin levels. In the same way, HbA1c and BSR/F levels also significantly varied with physical activity in T2DM patients; their respective p-values (0.0499 and 0.0021) also demonstrate the significant difference in their levels (Table 4).

Discussion

Our study's gender-specific demographic data shows that there are more female (67.5%) than male (32.5%) T2DM patients. The results counter what Sriram *et al.* found in 2001, which states that diabetes affects 2.3% of men and 1.4% of women.[10] The same results were obtained by Rao *et al.* in 2010.[11] Since this is a clinical study, its results may not apply to Pakistan in general; furthermore, the fact that it is a private

diabetic center introduces the possibility of referral bias. In our population study, gender-specific associations with cardiolipin indicate that cardiolipin levels are higher in males than in females. On the other hand, males have a positive attitude towards the disease and its management as compared to females due to anxiety, social worry, and stress to cope with the diabetes.[10] Another demographic variable is age. The highest prevalence of diabetes mellitus in our study was in the 41-50 age group (52.5%). Similar results were obtained by Mahar *et al*. in 2014.[12] In our study, there is a slight difference in cardiolipin levels, as there is an increase in cardiolipin levels with the aging process. These biases in results may be due to the unequal distribution of age groups or the small sample size. In our study, there is a decline in HbA1c levels with age. On the contrary, the HbA1c levels tend to increase with age, independent of diabetes status, as explained by Selvin *et al.* and Droumaguet *et al.*[13,14] We have noticed a decrease in the sampled population's blood sugar levels with aging. Ntaios *et al*. (2010) reported similar results,[15] finding an inverted J-shaped association between ages and fasting glucose levels, indicating a decline in glucose after a certain age in patients without diabetes. Changes can influence low blood sugar levels in metabolism, medication, diet, and overall health. Primary prevention is the main aim of preventing diabetes in susceptible individuals in the general population. A key component of controlling and managing T2DM is engaging in regular physical activity. The results on physical activity associated with different biochemical parameters, i.e., cardiolipin, HbA1c, and blood sugar levels, show a significant difference. However, there is a contradiction regarding HbA1c and blood sugar. Kiebish *et al*. (2010) suggest that insulin resistance and the etiology of diabetes may be linked to changes in cardiolipin.[16] The cardiolipin levels associated with their physical activity give referenced results, as there is a decline in cardiolipin levels with increased physical activity. The findings suggested that exercise training improved the cardiolipin profile, potentially enhancing mitochondrial function. Our study demonstrated a significant association between physical activity and glycemic control, including HbA1c levels and blood sugar.[17] Results of our sampled population indicated that in the high physical activity category, HbA1c and blood sugar levels increase, contrary to the results given by Colberg *et al*. (2016), who found that regular physical activity for individuals with diabetes has a positive impact on glycemic control.[18] When comparing the exercise group to the age group, the researchers found that the exercise group had significantly lower HbA1c values. Boniol *et al.* (2017) give an analysis demonstrating that moderate increases in physical activity are associated with significant reductions in fasting glucose and HbA1c.[3] While regular physical activity, whether low- or high-intensity, generally helps control cardiovascular complications and blood sugar levels,[1] there are instances in which exercise can temporarily raise blood sugar, particularly in people with diabetes. This phenomenon is known as the "exercise-induced hyperglycemia" or "the lag effect". Several factors contribute to this temporary rise in blood sugar during or after exercise. One key factor is the release of stress hormones, which can counteract insulin's effects, leading to an increase in blood sugar. Additionally, intense or prolonged exercise can cause the liver to release more glucose into the bloodstream. Type 1 diabetics' complicated glucose response to exercise was highlighted in a 2013 research article,[19] emphasizing the need for personalized approaches to manage blood sugar during physical activity. Exercise has been linked to increased cardiolipin content in younger individuals, potentially enhancing mitochondrial efficiency. Conversely, aging is associated with declining cardiolipin levels, and exercise may mitigate this decline by promoting mitochondrial biogenesis and function. Our research highlights the potential age-dependent impact of physical activity on cardiolipin levels, emphasizing its relevance to mitochondrial health. Increased cardiolipin levels can support improved mitochondrial function, enhancing energy production. This may positively impact overall energy metabolism and physical performance. On the other hand, decreased cardiolipin levels could compromise mitochondrial efficiency, potentially leading to fatigue and reduced energy output. Maintaining a balanced level of cardiolipin is essential for optimal cellular function and energy metabolism.

Conclusions

Our research highlights the potential age-dependent impact of physical activity on cardiolipin levels, emphasizing its relevance to mitochondrial health. A significant difference was also found between physical activity and blood sugar. Certain limitations also need to be acknowledged. Firstly, the sample size was relatively small and primarily focused on a specific demographic, limiting the generalizability of the findings. Future research should include larger, more diverse populations to yield more robust results. Additionally, investigating the long-term effects of physical activity on serum cardiolipin levels could provide a deeper understanding of the sustained benefits for diabetic patients.

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