

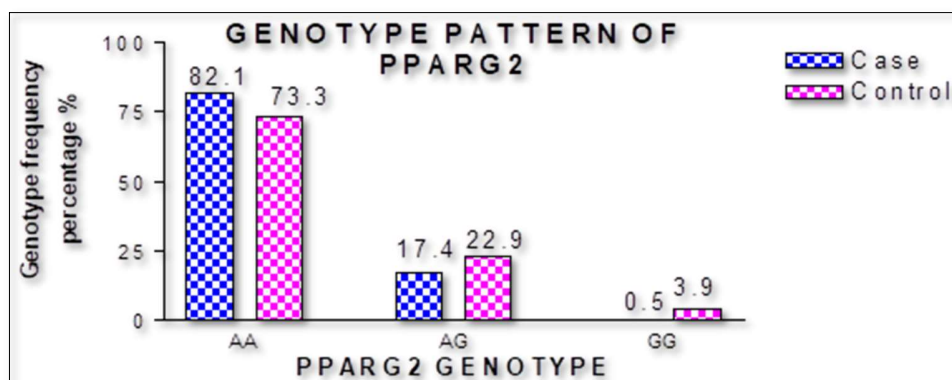
Table 4. Fisher Exact Test values of PPARG2 P12A polymorphism.

PPARG2 Genotype	Case		Control		P Value	Odds Ratio and CI
	N=190	N %	N=210	N%		
AA	156.0	82.11	154.0	73.3	0.0415*	1.668 (1.031 to 2.699)
AG	33.0	17.37	48.0	22.9	0.2127	0.7094 (0.4326 to 1.163)
GG	1.0	0.52	8.0	3.9	0.0390*	0.1336 (0.01654 - 1.079)
Alleles						
A	345	90.79	356	84.5	0.01**	1.772, (1.144 - 2.746)
G	35	09.21	64	15.5		0.5643, (0.3642- 0.8744)
Carriage Rate						
A	189	99.4%	202	96.2	0.0789	1.541 (0.9630 - 2.466)
G	34	17.89	56	26.7		0.6489, (0.4055 - 1.038)

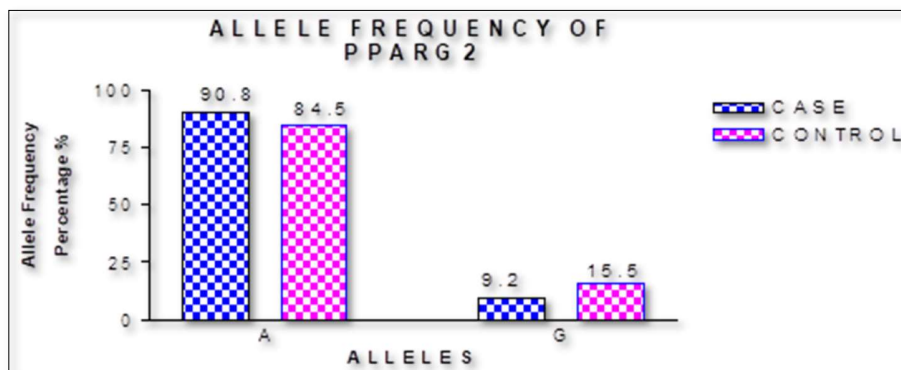
*Denotes the level of significant association between case and control

N-Number of individuals in study group

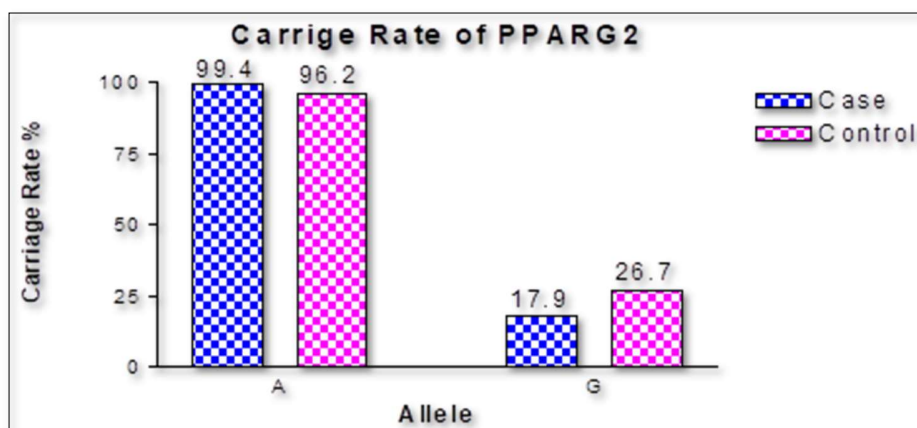
%-Genotype allele frequency and carriage rate expressed in percentage



Graph 1. Genotype distribution of PPARG2.



Graph 2. Allele Frequency of PPARG2.



Graph 3. Carriage Rate of PPARG2.

DISCUSSION

Weight gain has always been known to man to be a sign of good health and prosperity. Surplus energy stored as adipose tissue in the body depots has proved to be an efficient and practical way of making energy available for utilization by the body whenever it is needed [16,19]. Today, however, profound changes have occurred in our lives in association with improved living standards that have led to a markedly reduced need for utilization of stored energy and even for moderate levels of activity [23-26]. Consequently, the prevalence of weight gain and obesity are also rising and becoming a major public health problem in many countries of the world [27]. Table summarizes data on the prevalence of obesity in some developed and developing countries. The countries that have also been affected by these changes are the countries of the Middle Eastern Region. Within the last thirty years, most countries of the Middle East have experienced marked demographic, socio-economic, and life style changes. Traditional dietary habits have been modified due to the combined effect of westernized diets and population mixture, as well as the changes in lifestyle that encourage sedentary habits [28-32]. These changes have led to a profound alteration in the health and nutritional status of the concerned populations. Morbidity and mortality rates from infectious diseases and under-nutrition have decreased, to be replaced by rapidly rising rates of chronic non-communicable diseases such as NIDDM, CHD, and cancer. Furthermore, the sedentary life that has resulted from this improved socio-economic status, has led to an increase in the prevalence of overweight and obesity among populations in the Middle East [33-36]. In our results we found that rare ala allele 'G' was found to be in significantly low frequency in disease group as compared to Control group, whereas wild type allele 'A' was present in significantly high frequency in the disease group. These finding suggests that G allele may have a protective effect against pathophysiology of diabetes type 2. This study was done in small sample size but despite the sample size we found a strong relation with protection against diabetes type 2. Our study started from biochemical parameters related to

obesity. We found BMI in female (0.0388*) and WHR ($P < 0.0001^{***}$) having strong correlation to obesity. Biochemical parameter FPG (mg/dL) ($P < 0.0001^{***}$), Post-Prandial Glucose (mg/Dl) ($P < 0.0001^{***}$) were significantly associated to obesity. Gene PPARG2 having G and A alleles. The genotypic distribution of AA, AG is more than AA where p value is 7.253, (0.0266*). The allelic frequency of A is high in comparison to G alleles where p value is 6.684, (0.0097**) thus the carriage rate of A allele is high in comparison to G allele. In our study the ala allele is found significantly protective and was in healthy control in higher percentage as compared to Case (15.2 Vs 9.21%).

The PPARG2 gene abundantly expressed in adipose tissue has several variants, one of the most common (minor allele frequency of 10% in Caucasians) is the Pro12Ala substitution at codon 12 in PPARG2. This polymorphism has been shown to be associated with reduced ability to Trans-activate responsive promoters and thus with lower PPARG2 transcriptional activity [31-35]. The importance of PPARG2 in lipid, glucose and energy metabolism is well established. Since PPARG2 promotes adipocyte differentiation, it is an attractive candidate gene for states of altered triglyceride storage, such as obesity or conditions associated with underweight. Since the Pro12 allele is present in at least 80% of humans, the population attributable to risk of type 2 diabetes associated with this polymorphism is as high as 25% [6,13]. More consistently, the Pro12Ala polymorphism has been associated with a lower risk of type 2 diabetes in a meta-analysis of genome-wide association studies [33]. This gene is a confirmed type 2 diabetes susceptibility locus and is one of most 20 type 2 diabetes susceptibility loci identified over the last few years [32,36].

In our study population, odds ratio of mutant AA genotype was 0.13 and heterozygous AG was 0.70 these results suggest that PPARG2 Pro 12 Ala polymorphism could be protective against Obesity. The overall Odds ratio of less common 'A' allele was 0.56 which clearly indicates the possible protective role of PPARG2 Ala Allele.

REFERENCES

- Erdogan M, Karadeniz M, Eroglu Z, Tezcanli B, Selvi N, et al. (2007) The relationship of the peroxisome proliferator-activated receptor-gamma 2 exon 2 and exon 6 gene polymorphism in Turkish type 2 diabetic patients with and without nephropathy. *Diabetes Res Clin Pract* 78: 355-359.
- Olokoba AB, Obateru OA, Olokoba LB (2012) Type 2 diabetes mellitus: A review of current trends. *Oman Med J* 27: 269.
- Sanghera DK, Blackett PR (2012) Type 2 diabetes genetics: Beyond GWAS. *J Diabetes Metab* 3.
- Paramasivam D, Safi SZ, Qvist R, Abidin IBZ, Mohd Hairi NN, et al. (2016) Role of PPARG (Pro12Ala) in Malaysian type 2 diabetes mellitus patients. *Int Diabetes Dev Ctries* 36: 449-456.
- Pal A, McCarthy MI (2013) The genetics of type 2 diabetes and its clinical relevance. *Clin Genet* 83: 297-306.
- Zhu Z, Bakshi A, Vinkhuyzen AAE, Hemani G, Lee SH, et al. (2015) Dominance genetic variation contributes little to the missing heritability for human complex traits. *Am J Hum Genet* 96: 377-385.
- Bachtiar M, Sern Ooi BN, Wang J, Jin Y, Tan TW, et al. (2019) Towards precision medicine: Interrogating the human genome to identify drug pathways associated with potentially functional, population-differentiated polymorphisms. *Pharmacogenomics J* 19: 516-527.
- Tam V, Patel N, Turcotte M, Bossé, Pare G, et al. (2019) Benefits and limitations of genome-wide association studies. *Nat Rev Genet* 20: 467-484.
- Ingelsson E, McCarthy MI (2018) Human genetics of obesity and type 2 diabetes mellitus: Past, present, and future. *Circ Genom Precis Med* 11: e002090.
- Yen CJ, Beamer BA, Negri C, Silver K, Brown KA, et al. (1997) Molecular scanning of the human peroxisome proliferator activated receptor γ (hPPAR γ) gene in diabetic Caucasians: Identification of a Pro12Ala PPAR γ 2 missense mutation. *Biochem Biophys Res Commun* 241: 270-274.
- Radha V, Mohan V (2007) Genetic predisposition to type 2 diabetes among Asian Indians. *Indian J Med Res* 125: 259-274.
- Mori H, Ikegami H, Kawaguchi Y, Seino S, Yokoi N, et al. (2001) The Pro12 \rightarrow Ala substitution in PPAR-gamma is associated with resistance to development of diabetes in the general population: Possible involvement in impairment of insulin secretion in individuals with type 2 diabetes. *Diabetes* 50: 891-894.
- Motavallian A, Andalib S, Vaseghi G, Mirmohammad-Sadeghi H, Amini M (2013) Association between PRO12ALA polymorphism of the PPAR-[gamma]2 gene and type 2 diabetes mellitus in Iranian patients. *Indian J Hum Genet* 19: 239-244.
- Majid M, Masood A, Kadla SA, Hameed I, Ganai BA (2017) Association of Pro12Ala polymorphism of peroxisome proliferator- activated receptor gamma 2 (PPARgamma2) gene with type 2 diabetes mellitus in ethnic Kashmiri population. *Biochem Genet* 55: 10-21.
- Vergotine Z, Yako YY, Kengne AP, Erasmus RT, Matsha TE (2014) Proliferator-activated receptor gamma Pro12Ala interacts with the insulin receptor substrate 1 Gly972Arg and increase the risk of insulin resistance and diabetes in the mixed ancestry population from South Africa. *BMC Genet* 15: 10.
- Morales J, Welter D, Bowler EH, Cerezo M, Harris LW, et al. (2018) A standardized framework for representation of ancestry data in genomics studies, with application to the NHGRI-EBI GWAS Catalog. *Genome Biol* 19: 21.
- Raza ST, Abbas S, Ahmed F, Fatima J, Zaidi ZH, et al. (2012) Association of MTHFR and PPAR gamma 2 gene polymorphisms in relation to type 2 diabetes mellitus cases among north Indian population. *Gene* 511: 375-379.
- Szabo M, Máté B, Csép K, Benedek T (2018) Genetic approaches to the study of gene variants and their impact on the pathophysiology of type 2 diabetes. *Biochem Genet* 56: 22-55.
- Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, et al. (2018) Fine-mapping of an expanded set of type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* 50: 1505-1513.
- Mtiraoui N, Turki A, Nemr R, Ehtay A, Izzidi I, et al. (2012) Contribution of common variants of ENPP1, IGF2BP2, KCNJ11, MLXIPL, PPARgamma, SLC30A8 and TCF7L2 to the risk of type 2 diabetes in Lebanese and Tunisian Arabs. *Diabetes Metab* 38: 444-449.
- Zhu L, Huang Q, Xie Z, Kang M, Ding H, et al. (2017) PPARGC1A rs3736265 G>A polymorphism is associated with decreased risk of type 2 diabetes mellitus and fasting plasma glucose level. *J Med Chem* 8: 37308-37320.
- Bener A, Zirrie M, Al-Hamaq A, Nawaz Z, Samson N, et al. (2015) Impact of the Pro12Ala polymorphism of the PPARgamma2 gene on diabetes and obesity in a highly consanguineous population. *Indian J Endocrinol Metab* 19: 77-83.
- Badii R, Bener A, Zirrie M, Al-Rikabi A, Simsek M, et al. (2008) Lack of association between the Pro12Ala

- polymorphism of the PPAR-gamma 2 gene and type 2 diabetes mellitus in the Qatari consanguineous population. *Acta Diabetol* 45: 15-21.
24. Phani NM, Vohra M, Rajesh S, Adhikari P, Nagri SK, et al. (2016) Implications of critical PPARgamma2, ADIPOQ and FTO gene polymorphisms in type 2 diabetes and obesity mediated susceptibility to type 2 diabetes in an Indian population. *Mol. Genet. Genomics* 291: 193-204.
 25. Sanghera DK, Demirci FY, Been L, Ortega L, Ralhan S, et al. (2010) PPARG and ADIPOQ gene polymorphisms increase type 2 diabetes mellitus risk in Asian Indian Sikhs: Pro12Ala still remains as the strongest predictor. *Metab Clin Exp* 59: 492-501.
 26. Saleh R, Zahid ZI, Rahman MA, Jain P, Alam A, et al. (2016) Prevalence of PPAR-gamma 2 (rs1801282), RETN (rs3745367) and ADIPOQ (rs2241766) SNP markers in the Bangladeshi type 2 diabetic population. *Meta Gene* 10: 100-107.
 27. Meshkani R, Taghikhani M, Larijani B, Bahrami Y, Khatami S, et al. (2007) Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma2 (PPARgamma-2) gene is associated with greater insulin sensitivity and decreased risk of type 2 diabetes in an Iranian population. *Clin Chem Lab Med* 45: 477-482.
 28. Mato EPM, Pokam-Fosso PE, Atogho-Tiedeu B, Noubiap JJN, Evehe MS, et al. (2016) The Pro12Ala polymorphism in the PPAR-gamma2 gene is not associated to obesity and type 2 diabetes mellitus in a Cameroonian population. *BMC Obes* 3: 26.
 29. Malecki MT, Frey J, Klupa T, Skupien J, Walus M, et al. (2003) The Pro12Ala polymorphism of PPAR gamma 2 gene and susceptibility to type 2 diabetes mellitus in a Polish population. *Diabetes Res Clin Pract* 62: 105-111.
 30. Pei Q, Huang Q, Yang GP, Zhao YC, Yin JY, et al. (2013) PPAR-gamma 2 and PTPRD gene polymorphisms influence type 2 diabetes patients' response to pioglitazone in China. *Acta Pharmacol Sin* 34: 255-261.
 31. Mohamed MBH, Mtiraoui N, Ezzidi I, Chaieb M, Mahjoub T, et al. (2007) Association of the peroxisome proliferator-activated receptor-gamma 2 Pro12Ala but not the C1431T gene variants with lower body mass index in type 2 diabetes. *J Endocrinol Invest* 30: 937-943.
 32. Tariq K, Malik SB, Ali SHB, Maqsood ES, Azam A, et al. (2013) Association of Pro12Ala polymorphism in peroxisome proliferator activated receptor gamma with proliferative diabetic retinopathy. *Mol Vis* 19: 710-717.
 33. Clement K, Hercberg S, Passinge B, Galan P, Varrault-Vial M, et al. (2000) The Pro115Gln and Pro12Ala PPAR gamma gene mutations in obesity and type 2 diabetes. *Int J Obes* 24: 391.
 34. Avzaletdinova DS, Sharipova LF, Kochetova OV, Morugova TV, Erdman VV, et al. (2016) Association of variable rs1801282 locus of PPARG2 gene with diabetic nephropathy. *Russ J Genet* 52: 877-881.
 35. Wang F, Han XY, Ren Q, Zhang XY, Han LC, et al. (2009) Effect of genetic variants in KCNJ11, ABCC8, PPARG and HNF4A loci on the susceptibility of type 2 diabetes in Chinese Han population. *Chin Med J* 122: 2477-2482.
 36. Lv X, Zhang L, Sun J, Cai Z, Gu Q, et al. (2017) Interaction between peroxisome proliferator-activated receptor gamma polymorphism and obesity on type 2 diabetes in a Chinese Han population. *Diabetol Metab Syndr* 9: 7.