Original Research Article

Role of PPAR delta in Obesity and Type 2 Diabetes Mellitus due to Obesity

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Abstract

Background: Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear hormone receptor superfamily. The 3 PPAR isotypes, PPAR-alpha, PPAR-gamma, and PPAR-delta, play a key role in the regulation of lipid and glucose metabolism. Obesity and the interrelated disorders of the metabolic syndrome have become a major worldwide health problem. **Material and Method:** This study included 54 subjects with aim to study Role of Ppar delta in obesity and diabetes mellitus type 2 due to obesity. They were classified into: Group I: Included 15 apparently healthy lean individuals (7 males and 8 females) as control group. Their age ranged from 30 to 57 years, Group II: Included 15 obese non diabetic individuals (6 males and 9 females). Their age ranged from 21 to 65 years and Group III: Included 24 patients with type 2 diabetes mellitus with no diabetic complications (10 males and 14 females). Their age ranged from 33 to 60 years. This group divided into: Group IIIa: Diabetic non obese patients (12 patients) and Group IIIb: Diabetic obese patients (12 patients). **Result:** Comparison among carriers was found to be statistically significant, among all the parameters. **Conclusion:** Obesity and diabetes mellitus, critical danger factors for the advancement of CAD, are turning into a worldwide pandemic, which is identified with natural, social, and hereditary factors. Although changes in way of life are compelling in forestalling both diabetes and weight in high-hazard grown-ups with impeded glucose resilience, accomplishing alterations in way of life have shown to be difficult. The excitement for the utilization of PPARs is hosed by their possible oncologic impacts.

Keywords: Ppar delta, obesity & Type 2 DM.

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Introduction

Stoutness is an endocrine illness portrayed by unreasonable aggregation of fat tissue, whose event and suggestions result from the body failure to keep up with energy balance. This sickness is related to clinical issues (insulin obstruction, type 2 diabetes-DM 2, dyslipidemia, hypertension and cardiovascular infections), including ecological, hereditary and healthful variables, which, together, decide the Metabolic Syndrome (MS)[1]. Peroxisome proliferator-enacted receptors (PPARs) are among the cycles which permit the transformation of metabolic and useful reactions to extracellular signs. Logical proof recommends that PPAR can be engaged in medicines possibly successful against MS, when it appears to be that there is a connection between the pretended by these receptors and MS[2]. The current plans to depict the sub-atomic instruments associated with the action of the PPARs family on the digestion of lipids, sugars and proteins, and their impact on corpulence and diabetes[3].

PPARs are ligand-initiated record factors and have a place with the atomic receptor superfamily. PPARs direct record of target qualities by shaping heterodimers with the retinoid X receptor (RXR) and restricting to explicit PPAR reaction components (PPREs) in the advertiser area of target genes[4].

Without a trace of ligands, PPAR/RXR heterodimers can effectively curb record through the enrolment of corepressor edifices that contain atomic receptor corepressor as well as quieting arbiter for retinoid and thyroid receptors within the sight of ligands, PPAR/RXR heterodimers enact record through the enlistment of coactivator proteins[5].

In addition, PPARs can likewise subdue quality articulation by threatening the exercises of other sign ward record factors, for example, NF-B and activator protein 1.50 Three isoforms, encoded by discrete qualities, have been distinguished: PPAR-, PPAR-, and PPAR-/(from now on alluded to as PPAR-), what share 60% to 80% homology in their ligand-and DNA-restricting areas[6]. Unsaturated long-chain unsaturated fats, just as their eicosanoids subsidiaries are endogenous ligands for every one of the 3 of the PPAR isotypes. Synthetic ligands for 2 types of the receptor, PPAR-and PPAR-, have been produced for clinical use; ligands for PPAR-are right now under clinical turn of events. Each PPAR receptor subtype shows unmistakable examples of articulation and covering however particular natural activities. While PPAR-and PPAR-are overwhelmingly present in liver and fat tissue, separately, PPAR-is ubiquitiously expressed[7].

Diabetes mellitus is a gathering of metabolic issues described by hyperglycemia coming about because of imperfection in insulin emission, insulin activity or both. The pathogenesis of type 2 diabetes is multi-layered including both way of life and hereditary part. Insulin obstruction in fringe tissues is a high-hazard factor and constantly goes before the advancement of plain sort 2 diabetes. Insulin obstruction is related with weight particularly when midway dispersed[8].

Material & Method

This study included 54 subjects. They were classified into: Group I: Included 15 apparently healthy lean individuals (7 males and 8 females) as control group. Their age ranged from 30 to 57 years, Group II: Included 15 obese non diabetic individuals (6 males and 9 females). Their age ranged from 21 to 65 years and Group III:

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Included 24 patients with type 2 diabetes mellitus with no diabetic complications (10 males and 14 females). Their age ranged from 33 to 60 years. This group divided into: Group IIIa: Diabetic non obese patients (12 patients) and Group IIIb: Diabetic obese patients (12 patients).

All subjects in this study were subjected to full history taking especially the age of onset of diabetes mellitus in group III, duration of the disease and regimen of the treatment, full clinical examination with measuring the body weight and length for estimation of BMI which is calculated as body weight (BW, kg) divided by body height (BH, m2). Obesity is defined as a (BMI) of ≥ 30 kg/m2 and overweight is defined as (BMI ≥ 25 kg/m2). Peripheral blood samples were collected from fasting patients and controls. Each sample was divided into 2 mL in blank tube for separation of serum for estimation of fasting glucose level and serum insulin hormone level, and 3 mL in sterile vacuum tubes containing EDTA for DNA extraction and studying of PPAR-g2 gene polymorphism. 2-h post prandial blood samples were also collected for glucose estimation.

Results

Table 1: Phenotypic characters of the studied groups

	Group I	Group II	Group IIIa	Group IIIb	
Age Range (year) Mean±SD	30-57 44.8± 8.1	21-65 43.5± 14	35-60 47.4± 7.8	33-56 46.2± 6.5	p= 0.75
Sex Male Female	7 8	6 9	5 7	5 7	p= 0.98
BMI Range (kg/m2) Mean±SD	20–29 23 ± 2.4	37–53 42±5	22.5 - 28.2 25.7 ± 1.6	30.5 – 47 42.4 ± 4.6	<0.001
Fasting bl. glucose Range(mg/dl) Mean±SD	60 - 90 64.8± 5.35	65 - 95 69.09 ± 5.6	90 - 120 98.79 ± 9.69	95 - 125 104.76± 9.6	<0.001
Post prandial glucose. Range (mg/dl) Mean±SD	100-130 105.34 ±10.38	105 – 135 112.36 ± 10.97	148 - 187 154.4 ± 12.5	158 – 210 166.6 ± 12.3	<0.001
Fasting Insulin. Range (µu/ml) Mean±SD	5.9 -10 7.98 ± 1.1	10 -15 12.4 ± 1.6	11.2 - 14.5 12.8 ± 1.14	12 -15.5 14.57 ± 0.99	<0.001

BMI: Body Mass Index HOMA-IR homeostasis model assessment of insulin resistance.

Table 2: Lipid profile of the studied groups

Lipid profile	Group I	Group II	Group IIIa	Group IIIb	p-value
Cholesterol	211.01±18.1	231.12 ±17.5	241.01±18.2	281.01 ±19.2	<0.001
Triglycerides	149.7 ±12.1	150.1 ±11.3	268.9±12.4	279.2 ±13.1	<0.001
HDL	42.9 ±3.1	43.1 ±4.2	40.6 ±4.1	37.9 ±3.9	<0.048
LDL	126.2 ±8.9	127.2 ±8.9	117.6 ±9.2	128.3 ±9.4	<0.001
VLDL	158.3 ±9.3	159.1 ±11.4	147.8 ±12.1	159.6 ±13.2	<0.037

Table 3: Comparison of fasting blood glucose (mg/dl), serum insulin (µu/ml) in the studied groups according to PPAR genotype distribution

	Fasting blood glucose (mg/dl)		Fasting serum insulin (µu/ml)	
	Pro/Pro carriers	Pro/Ala (Pro allele) + Ala/Ala	Pro/Pro carriers	Pro/Ala + Ala/Ala carriers
	Mean±SD	Mean±SD	Mean ±SD	Mean ±SD
Group I	65±7.1	73±0.42	7.1 ± 1.1	6.5±1.2
Group II	79±13.2	81±0.55	13.2±1.2	11.13±1.3
Group III	90.8±13.7	102.1 ±0.8	13.7±1.5	11.9±1.7
P-value	<0.034	<0.04	<0.021	<0.049

Discussion

Inside PPAR examination, fundamental and translational clinical methodologies brought about new ideas that can be made an interpretation of and tried into clinical practice sooner rather than later. The accompanying segment of this survey examines some new applications and new ideas of PPAR science[9].

PPARδ (also known as PPARβ) is ubiquitously expressed and when activated it promotes fatty acid oxidation, thermogenesis, insulin sensitivity, high density lipoprotein cholesterol (HDLc) levels in plasma and overall energy expenditure[10]. PPARδ deficient mice are prone to obesity and insulin resistance when challenged with a high-fat diet (HFD). Conversely, transgenic expression of a constitutively active form of PPARδ in adipose tissue or skeletal muscle protects mice from diet-induced obesity and regulates muscle fiber type switching, respectively[11].Although PPAR δ are ubiquitously expressed, expression in adipose, skin, skeletal muscle and cardiac tissues is considered to have the greatest clinical value. Expression of PPAR δ is increased by fasting, fatty acids (thus serves as a lipid sensor) and exercise [12]. PPAR/ may upregulate PPAR expression and trigger PPAR δ -activated lipid metabolism. The number of HDL particles, apoAI, apoA-II and apoA-III are all increased with PPAR δ receptor activation [13]. Accumulating evidence has defined a role of PPAR δ in cholesterol transporter ABCA1 expression and down-regulation of Niemann-Pick C1-like gene involved in intestinal cholesterol absorption [14]. This may serve as a possible explanation for PPAR δ mediated increase in HDL although further study is warranted to better elucidate the anti-dyslipidemia effect offered by PPAR δ activation[15].The role of PPAR δ in glucose metabolism has not been precisely delineated. It appears that PPAR/ ligands may improve insulin sensitivity by facilitating fatty acid oxidation in the adipose, skeletal and cardiac tissues [16]. PPAR δ activates -oxidation courtesy of its targeting on gene Pdk4 that inhibits pyruvate dehydrogenase complex which decreases glucose oxidation. Another possible mechanism is reported to be mediated through pentose phosphate shunt activation [17].

Although PPARδ is abundantly expressed along the entire intestinal tract, its potential role in energy homeostasis in this organ has not been well explored[18]. Daoudi *et al*. showed a role of intestinal PPARδ in the stimulation of post-prandial glucagon-like protein-1 (GLP1) production in enteroendocrine L-cells, resulting in preservation of β-cell morphology and function and, thereby, increased systemic insulin sensitivity[18]. In the present study we evaluated a possible role of PPARδ in the intestine in energy metabolism and the development of metabolic syndrome using mice with an intestinal epithelial specific deletion of the *PPAR*δ gene. Here we show that intestinal PPARδ contributes to the protection against diet-induced obesity and that intestinal PPARδ is required for mediating the increase in plasma levels of HDLc by PPARδ activation[19].

Conclusion

Obesity and diabetes mellitus, critical danger factors for the advancement of CAD, are turning into a worldwide pandemic, which is identified with natural, social, and hereditary factors. Although changes in way of life are compelling in forestalling both diabetes and weight in high-hazard grown-ups with impeded glucose resilience, accomplishing alterations in way of life have shown to be difficult.

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