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# Lipids in the Pathogenesis of Benign Prostatic Hyperplasia: Emerging Connections

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## 1. Introduction

Benign prostatic hyperplasia (BPH) is a common melody of the aging men characterized by noncancerous enlargement of the prostate gland and is often associated with lower urinary tract symptoms (LUTS) (Berry et al., 1984). Approximately, 60 percent of men aged over 50 years have histological evidence of BPH and, after the age of 70, the proportion increases to 80 percent (Berry et al., 1984). It is a chronic, progressive and highly prevalent disease, clinically manifests as LUTS, posing a socioeconomic burden to the patients (Saigal and Joyce, 2005). Recently, Stranne et al., reported that one-third of the Swedish male population aged over 50 years have LUTS, which is often associated with BPH (Stranne et al., 2009). BPH is rarely fatal, but affects the quality of life, and if left untreated, serious life-threatening complications may arise. Prostatic growth and development are governed by the genetic (Sanda et al., 1994), hormonal (Marker et al., 2003) and dietary factors (Bravi et al., 2006). Although, its etiology is not well understood, several theories have been proposed to explain the pathogenesis of BPH (Alberto et al., 2009; Bosch, 1991; Srinivasan et al., 1995). Augmented steroidal signaling and mesenchymal-epithelial interactions are required for the normal as well as pathological growth of the prostate gland (Marker et al., 2003). However, current literature indicates that apart from steroids, peptides and lipids are also playing a crucial role in the pathogenesis of BPH (Cai et al., 2001; Culig et al., 1996; Escobar et al., 2009; Kaplan-Lefko et al., 2008; Rahman et al., 2007; Rick et al., 2011; Story, 1995; Vikram and Jena, 2011a; Vikram et al., 2010c). Even if the effects of peptides and lipids on the growth of the gland is milder as compared to that of steroids, chronic change in their levels either due to dietary habit or genetic predispositions can significantly contribute to the initiation and/or progression of the disease over a period of time. Existing clinical/epidemiological and preclinical studies provide convincing evidence for the association between insulin-resistance, metabolic disorder and type 2 diabetes with the BPH (Francisco and Francois, 2010; Vikram et al., 2010a; Wang and Olumi, 2011). Previous experimental studies in our laboratory suggested that insulin-resistance associated secondary rise in the plasma insulin level plays a central role in the prostatic enlargement (Vikram and Jena, 2011b; Vikram et al., 2010a; b; 2011a; Vikram et al., 2010c; Vikram et al., 2011b). Other peptides such as insulin-like growth factor-I (IGF-I), IGF-I binding proteins (IGFBPs), growth hormone (GH), transforming growth factor-β (TGF-β) family proteins are reported to have important

implications in the prostatic growth (Culig et al., 1996; Ikeda et al., 2000; Rick et al., 2011; Vikram et al., 2010c). However, information on the role of lipids in the prostatic growth is scarce and there is a need of further research in this area. Nevertheless, existing in-vitro, in-vivo and clinical/epidemiological studies suggests that apart from contributing to the development of insulin-resistance and secondary hyperinsulinemia, lipids has a direct role in the normal prostatic growth and pathogenesis of the BPH.

## 2. Role of lipids in transcriptional regulation

Lipids are conventionally known as an important constituent of the biological membranes and as a signaling molecule in the cytoplasm. The presence of lipids in the nucleus and identification of phosphotidylinositol (PtdIns)-4-kinse activity in the preparation that were enriched in nuclear membranes (Smith and Wells, 1983a; b), and identification of PtdIns-4-phosphate and PtdIns-4,5-bisphosphate that were differentially metabolized from lipids in the cytoplasm provided early evidence for the nuclear lipid signaling (Irvine, 2003). A recent study by Lee et al., explores the nuclear activities of lipids, showing that dilauroyl phosphotidlycholine controls transcriptional program through nuclear-receptor dependent pathway (Ingraham, 2011; Lee et al., 2011). The study was of particular interest as phosphotidylcholine reversed some of the consequences of high-fat diet feeding (Lee et al., 2011), which is known to promote the cellular proliferation, contractility and overall enlargement of the prostate in rodents (Vikram et al., 2010c). The nuclear signaling and transcriptional regulation by lipids implies that targeting nuclear lipid signaling might be of value in finding the answers for the diseases associated with dietary habit and sedentary lifestyle such as insulin-resistance, type 2 diabetes, several cancers and BPH.

## 3. Insulin-resistance and BPH

The main function of insulin includes regulation of glucose uptake, glycogenesis and tight control of the plasma glucose level (Vikram and Jena, 2010). Insulin-resistance is a condition in which normal level of insulin elicits subnormal response. It is a condition which is associated with a group of disorders such as obesity, dyslipidemia, elevated fasting glucose level, hyperinsulinemia and hypertension. In addition to the type 2 diabetes and cardiovascular diseases, patients with insulin-resistance syndrome are at higher risk of BPH (Kasturi et al., 2006). Possible implications of the diabetes, insulin-resistance and insulin-resistance associated disorders in the pathogenesis of BPH have been previously reviewed, and interested readers are encouraged to read the concerned articles for more information (Vikram et al., 2010a; Wang and Olumi, 2011).

## 4. Fatty acids, dietary fat and BPH

Strong appetite for the sugar, fat, and salt might have been adaptive for our ancestors, as they had very little access to sweet, fatty and salty foods. We have inherited these appetites and have easy access to these foods. As a consequence many of us suffer from obesity, high blood level of lipids, insulin-resistance, diabetes, hypertension, heart disease, several types of cancer and other aging-related disorders, including BPH. Sedentary lifestyle and fat-rich diets are considered as major contributor to the rise in the incidences of metabolic disorders. Over the past 60 years in USA, the ratio of dietary intake of ω-6-FA verses ω-3-FA has

increased from 2:1 to 25:1 (Simopoulos, 1999), and animal fat is a major source of ω-6-FAs which has been found to be associated with the higher risk of LUTS and BPH (Maserejian et al., 2009; Suzuki et al., 2002). Considering the rise in the incidence of LUTS/BPH in the obese and insulin-resistant individuals, it becomes increasingly important to understand the role of lipids in the pathogenesis of disease.

### 4.1 Evidence from in-vitro experiments

Limited information is available on the direct role of fatty acids (FAs) in the growth of normal and benign prostatic cells, as most of the studies have been conducted on the prostate cancer cell lines. However, cancer cell lines studies have indicative value for the potential effects of these FAs, as like prostate cancer, BPH is also associated with the pathological increase in the cell proliferation. A recent report indicating dominant uptake of FAs by the prostate cells [non-malignant (RWPE-1) as well as malignant (LnCaP and PC-3)] suggests their important role in the growth and development of the gland (Liu et al., 2010). Pandalai et al., reported growth promoting effects of ω-6-FAs on the rat non metastatic epithelial cell lines (EPYP1 & EPYP2), rat metastatic cell line (Met-Ly-Lu), and human metastatic prostate cancer cells (PC-3, LnCaP & TSU) (Pandalai et al., 1996). Arachidonic acid, a ω-6-FA treatment led to accelerated growth of the PC-3 cells in-vitro (Ghosh and Myers, 1997). Further, Rose et al., reported concentration-dependent stimulation of PC-3 cells by the linolenic acid (ω-6-FA) and inhibition with the eicosapentanoic acid and docosahexanoic acid (ω-3-FAs) (Rose and Connolly, 1991). Further, long term eicosapentanoic acid treatment has been found to inhibit the metastatic activities of the PC-3 cells (Rose and Connolly, 1991). Recently, we investigated the effects of the serum of high-fat diet-fed (saturated animal fat-lard) rats on the growth of PC-3 cells, and a significant acceleration in the growth was observed (Vikram and Jena, 2011a). The serum characteristics of these rats indicated a rise in the glucose, triglyceride, cholesterol and insulin levels. Although, rise in the insulin level appears to be the primary cause for the accelerated growth of the cells owing to the mitogenic effects of the hormone, the possibility of direct growth promoting effects of lipids cannot be denied. Taken together, these studies suggest that at least ω-6-FAs have a growth stimulating effects on the prostatic cells, and thus represent a potential risk factor for BPH.

### 4.2 Evidence from in-vivo experiments

The study by Cai et al., provided first evidence for the prostatic growth promoting effects of dietary fat in rats (Cai et al., 2001). Similarly, Rahman et al., observed enlargement of the ventral prostate and increased expression of alpha-adrenergic receptors in the hyperlipidemic rats (Rahman et al., 2007). Further, inclusion of the saturated animal fat (lard) in the diet induced prostatic enlargement and changed the expression of androgen receptor and peroxysome proliferator activated receptor γ (PPARγ) (Escobar et al., 2009). Polyunsaturated FAs are ligands for the PPARγ, which is involved in the regulation of cell differentiation and proliferation (Morales-Garcia et al., 2011; Parast et al., 2009), and therefore appears to represent a possible link between diet and prostatic growth (Escobar et al., 2009). Prostatic atrophy and increased apoptosis in the hypoinsulinemic rats (induced by selective β-cell toxins, either streptozotocin or alloxan) further supports the view that insulin plays a central role in the prostatic growth and development (Arcolino et al., 2010; Ikeda et al., 2000; Suthagar et al., 2009; Vikram et al., 2011b; Vikram et al., 2008; Yono et al., 2008;

Yono et al., 2005). Increased cell proliferation and enlargement of ventral prostate in rats kept on the diet rich in saturated fat was observed (Vikram et al., 2010b; 2011a; Vikram et al., 2010c). Interestingly, pioglitazone (a synthetic PPARγ receptor agonist) treatment led to decreased cell proliferation, increased apoptosis and restoration of prostatic weight in the diet-induced insulin-resistant rats (Vikram et al., 2010b; Vikram et al., 2010c). This observation can be explained on the basis of the restoration of insulin-sensitivity and secondary hyperinsulinemia as pioglitazone is known to improve the insulin-sensitivity (Vikram and Jena, 2010). Further, increased oxidative stress and incidence of prostatic adenocarcinoma and hyperplasia was observed in the rats kept on high-cholesterol diet for long time (80 – 100 weeks) (Homma et al., 2004). Increased expression of NADPH oxidase subunits, activation of NF-kB signaling and decreased expression of glutathione peroxidase 3 clearly indicated the increased oxidative stress and activation of inflammatory response in ventral prostate of the HFD-fed rats (Sekine et al., 2011; Vykhovanets et al., 2011). Inflammation has been greatly implicated as a risk factor for the development of BPH (Abdel-Meguid et al., 2009; Chughtai et al.; Donnell, 2011; Kim et al., 2011a; Wang et al., 2008). Despite a marginal decrease in the weight of the prostate in ACI/seg rats an significant increase in the expression of 5-α-reductase 2 mRNA level was observed in the high-fat diet-fed rats (Cai et al., 2006). Based on these evidences from animal studies it appears that (i) insulin-resistance associated secondary hyperinsulinemia, (ii) activation of PPARγ signaling by FAs and (iii) increased prostatic inflammation are the important nodes for further investigative studies.

### 4.3 Evidence from clinical/epidemiological studies

Presence of dyslipidemia in the BPH patients is a frequently noted condition under clinical setups (Nandeesha et al., 2006). High level of total cholesterol, LDL-cholesterol, triglyceride, decreased level of HDL-cholesterol increases the risk of BPH, and cholesterol-lowering medication may reduce the risk (Moyad and Lowe, 2008). Yang et al., compared FA profiles in the serum of patients with prostate cancer and BPH and proposed that polyunsaturated FAs have certain relation with BPH and prostate cancer (Yang et al., 1999). Higher serum LDL is associated with greater risk of BPH (Parsons et al., 2008), and physical activity, which is known to decrease the serum lipid level is associated with the decreased risk for BPH (Parsons and Kashefi, 2008). Hyperlipidemia is closely associated with the obesity, higher body mass index (BMI), and these parameters show a positive correlation with the BPH (Dahle et al., 2002; Hammarsten and Hogstedt, 1999; Hammarsten et al., 1998; Parsons et al., 2006; Parsons et al., 2009). Kim et al., reported that the patients with more BMI tend to have larger prostate volume and higher International Prostate Symptom Score (Kim et al., 2011b). Several studies indicate that obesity and sedentary lifestyle substantially increases the risk for BPH (Dahle et al., 2002; Parsons, 2011; Parsons et al., 2006; Parsons et al., 2009). Recently, it has been reported that the central obesity is a better predictor of LUTS (Kim et al.; Lee et al., 2009). In a health professionals follow up study a moderate association between FAs intake and risk of BPH was observed (Suzuki et al., 2002). A cross-sectional study of 1545 men aged 30-79 years in the Boston Area Community Health Study the associations between dietary intakes of total energy, carbohydrates, protein, fat, cholesterol and LUTS in men was examined (Maserejian et al., 2009). Results indicated that high-energy intake was associated with higher LUTS symptoms and the storage symptoms increased with the higher fat intake

(Maserejian et al., 2009). Further, Kristal et al., reported significant increase in the symptomatic BPH with higher total fat intake and polyunsaturated fats, and showed a significant decrease in the symptomatic BPH with high-protein intake and alcohol consumption (Kristal et al., 2008). Leptin and adiponectin are closely associated with the obesity, and effort has been made to identify the relationship, if any, between these mediators and the risk of BPH. Although, no association has been observed between plasma leptin level and BPH (Hoon Kim et al., 2008; Lagiou et al., 1998), high plasma adiponectin concentrations were found to be associated with the reduced risk of symptomatic BPH (Schenk et al., 2009). Few independent studies indicate that obesity is associated with hyperinsulinemia, which in turn promotes the prostatic growth and risk for BPH (Becker et al., 2009; Kogai et al., 2008; Vogeser et al., 2009). In contrast, few reports argue that, obesity is associated with increased estrogen/androgen ratio and sympathetic activity, both individually hypothesized to promote the development of BPH (Giovannucci et al., 1994). Obesity can augment prostatic growth either by (i) promoting the development of insulin-resistance and secondary hyperinsulinemia or by (ii) increasing the estrogen/androgen ratio. In contrast, isolated report indicates an inverse association between obesity and BPH owing to reduced testosterone level in the obese people (Zucchetto et al., 2005). However, further studies investigating the relationship between plasma FAs level, obesity, BMI and prostatic growth are needed to shed light on the pathogenesis of BPH. Although, systematic clinical studies have not been performed to evaluate the effect of lifestyle modifications on the BPH outcomes, number of studies supports the view that heart-healthy lifestyle changes would have beneficial effect on the prostatic health and will eventually improve the quality of life of patients.

## 5. Emerging mechanistic connections

### 5.1 Autotaxin-lysophosphatidic acid pathway

Lysophophatidic acid (LPA) is a small water soluble phospholipid, which binds to its G-protein coupled receptors and activates several downstream signaling pathways (Berdichevets et al., 2010; Rancoule et al., 2011). It is primarily produced by the activity of the phospholipase autotaxin (ATX) (Van Meeteren and Moolenaar, 2007). Excessive fat intake is associated with adiposity, development of insulin-resistance and obesity, and these conditions are known to increase the expression of ATX, and therefore the LPA levels (Ferry et al., 2003). Recent study indicating the expression of LPA-related molecules in the prostate (Zeng et al., 2009) suggests that LPA might have an important role in the normal prostatic growth and pathogenesis of the BPH (Sakamoto et al., 2004). Kulkarni et al., proposed ATX-LPA axis as a possible link between excessive dietary fat intake and prostatic hyperplasia (Kulkarni and Getzenberg, 2009). LPA is involved in the inflammatory responses and experimental studies indicating increased oxidative stress and NF-kB activation in the ventral prostate of high-fat diet-fed rodents (Sekine et al., 2011; Vykhovanets et al., 2011), which are known to develop prostatic enlargement (Vikram et al., 2010b; 2011a; Vikram et al., 2010c) supports the hypothesis. Further, clinical studies indicate that systemic inflammation or lower level of soluble receptors that bind to the inflammatory cytokines increase the BPH risk (Schenk et al., 2010). The pharmacological inhibitors of ATX such as S32826 (Ferry et al., 2008) and ongoing efforts of medicinal chemists (North et al., 2010; North et al., 2009; Parrill and Baker, 2010) in this direction might provide an answer to therapeutic management of the BPH.

### 5.2 PPARγ signaling

PPARs are ligand activated transcription factors, which includes polyunsaturated FAs, eicosanoids, prostaglandins, docosahexaenoic acid, thiozolidinediones, and non-steroidal anti-inflammatory drugs. A recent study by Jiang et al., showed that conditional prostatic epithelial knockout of PPARγ resulted in the inflammation and focal hyperplasia which developed into prostatic intraepithelial neoplasia (Jiang et al.). Increased expression of PPARγ and overall enlargement of the prostate was observed in the rats kept on diet rich in saturated fat (Escobar et al., 2009). We also observed increased cell proliferation and prostatic enlargement in rodents kept on high-fat diet (Vikram et al., 2010b; 2011a; Vikram et al., 2010c). Moreover, pioglitazone (a PPARγ agonist) treatment restored prostate size in these rats (Vikram et al., 2010b; Vikram et al., 2010c). A recent study indicating the dominant uptake of FAs (as compared to glucose) by the malignant as well as non-malignant prostatic cells (Liu et al., 2010) underlines the possible role of PPARγ in the prostatic growth and development. These findings suggest that PPARγ represents a potential link between dietary fat and prostatic growth. However, further studies are needed to characterize its role in the normal and pathological growth of the prostate.

### 5.3 Hyperinsulinemia: Altered insulin/IGF signaling

Hyperinsulinemia generally develops as a compensatory response to the decreased insulin mediated actions under the insulin-resistant conditions (McKeehan et al., 1984). Experimental (Cai et al., 2001; Escobar et al., 2009; Rahman et al., 2007; Vikram et al., 2010a; b; 2011a; Vikram et al., 2010c) and clinical/epidemiological (Hammarsten et al., 2009; Hammarsten and Hogstedt, 2001; Nandeesha et al., 2006) studies indicate that the hyperinsulinemia is an independent contributor to the prostatic cell proliferation and pathogenesis of the BPH. Further, hyperinsulinemic condition can contribute to the augmented prostatic growth by several ways such as (i) increasing the serum level of IGF-I (Chokkalingam et al., 2002; Nam et al., 1997), (ii) possibility of the binding of insulin with the IGF-I receptor (IGF-IR) under the hyperinsulinemic conditions and (iii) binding of IGF-I to the insulin receptor (IR) (Belfiore and Frasca, 2008; Li et al., 2005). Further, IR has two isoforms, A and B, the former is having metabolic as well as mitogenic effects while B is mainly concerned with the metabolic effects. IR isoforms exhibit difference in the binding affinities to the ligand(s) and downstream signaling cascade (Giudice et al., 2011; Kosaki et al., 1995; Leibiger et al., 2001; Sciacca et al., 2003; Uhles et al., 2003; Vogt et al., 1991). IGF-II binds to the IR-A and mediates its growth promoting effects but not with IR-B (Frasca et al., 1999; Morrione et al., 1997). This means that insulin, IGF-I and IGF-II competes to bind with the IR-A, while only insulin binds with the IR-B. The hybrid receptors, IR-A/IR-B and IR/IGF-I further complicates the molecular diversification of the insulin signaling system. IR-A/IR-B hybrid receptors were found to bind to both insulin and IGF-II and therefore, resemble IR-A homodimers rather IR-B homodimers (Blanquart et al., 2008). The IR/IGF-IR hybrid receptors (Pandini et al., 2002; Soos et al., 1990) are activated by both insulin as well as IGF-I, but the IGF-I effect is predominant, and it resembles IGF-1R homodimers rather IR homodimers (Langlois et al., 1995). The IGF and insulin signaling system has been summarized in figure 1. Prostate is known to have both isoforms of the IR (Cox et al., 2009). Experimental studies investigating the effect of dietary habits (particularly dietary fat) on the expression of IR isoforms and signaling kinetics might provide valuable insight in the understanding of the pathogenesis of the BPH under the insulin-resistant, obese and diabetic conditions.

### 5.4 Estrogen/androgen ratio

Androgen deprivation leads to rapid apoptosis of the luminal secretory cells and atrophy of the prostate gland (Ikeda et al., 2000; Vikram et al., 2010c; Vikram et al., 2008). However, with the re-administration of the androgens prostate regains its normal size, and is capable of more than 15 rounds of the regression / regeneration cycle (Wang et al., 2009). Further, administration of either estrogen or dihydrotestosterone leads to hyperproliferation and induction of prostatic hyperplasia in the experimental animals. These simple experiments highlights the crucial role of steroidal hormones in the growth and development of the gland. Aromatase is a CYP450 enzyme which irreversibly converts testosterone to the estradiol, and obesity is associated with increased aromatase activity (Subbaramaiah et al., 2011). Increased aromatase activity in the obese people may lead to rise in the estrogen/androgen ratio and hence the susceptibility for developing BPH. These aspects have been recently reviewed by Nicholson et al., and readers are encouraged to read the review (Nicholson and Ricke, 2011).

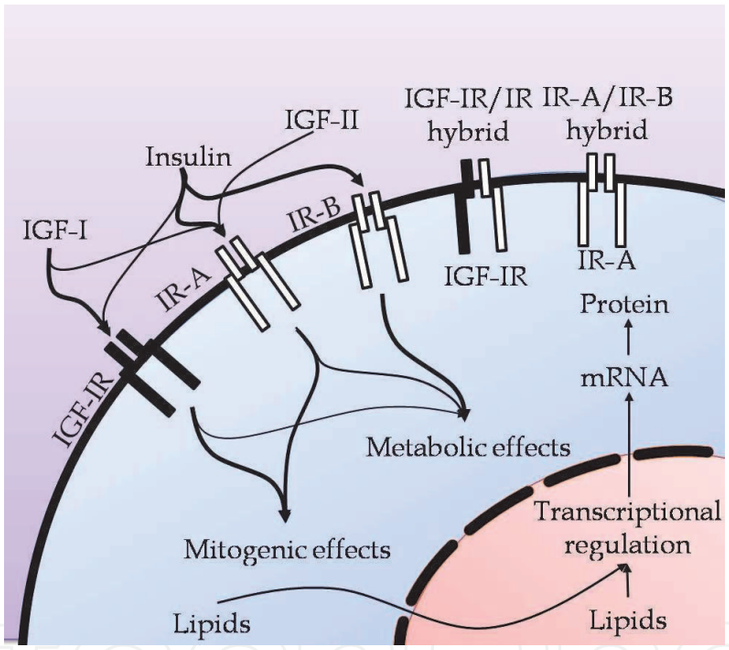


Fig. 1. The IGF and insulin receptor signaling system. To avoid confusion, the binding affinity of the ligands and relative effects of hybrid receptors (metabolic and mitogenic) are not depicted in the figure. However, the IGF-IR/IR hybrid resembles IGF-IR homodimer and IR-A/IR-B resembles IR-A homodimers. Lipids are involved in nuclear signaling and can influence transcriptional regulation and thus growth and differentiation. IGF-I/II; insulin-like growth factor-I/II, IGF-IR; insulin-like growth factor-I receptor, IR-A/B; insuln receptor isoform-A/B.

## 6. Summary

BPH is a highly prevalent condition of prostate in the aging men population. The worldwide increase in the prevalence of BPH has been thought to be associated with obesity and lifestyle changes such as excessive intake of fat-rich diet and physical inactivity. Considering

the changing dietary habits and rising incidences of BPH, it becomes increasingly important to delineate the precise roles of lipids in the normal as well as pathological growth of the prostate. Although, experimental and clinical/epidemiological studies suggest that these conditions contribute to the pathogenesis of both insulin-resistance and BPH, the direct role of lipids in the pathogenesis of prostatic enlargement is far from complete understanding. Role of lipids in the progression of insulin-resistance and other disorders and indirect effect on the prostatic growth owing to compensatory rise in the plasma insulin level is essentially correct, but what has emerged is that the lipids might have a direct influence on the normal as well as pathological growth of the prostate.

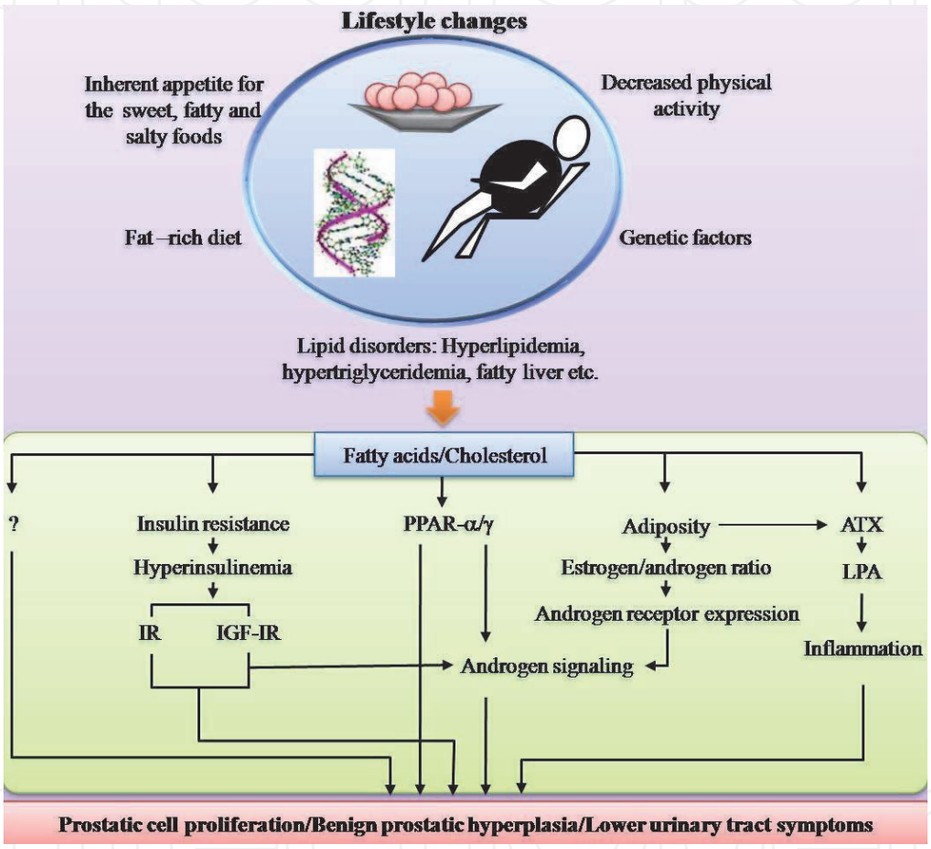


Fig. 2. Modern lifestyle associated changes including increased consumption of fat-rich diets and decreased physical activities contributes to the development of lipid-disorders and obesity. The present illustration demonstrates the possible influence of these factors on the prostatic growth and development. IR; insulin receptor, IGF-IR; insulin-like growth factor-1 receptor, PPAR-α/γ; peroxisome-proliferator activated receptor alpha/gamma, ATX; autotaxin, LPA, lysophosphatidic acid.

## 7. Conclusion

In addition to the genetic factors, environmental factors such as physical inactivity and excessive intake of dietary fat contribute to the increased incidence of lipid-disorders and obesity worldwide. These factors directly as well as indirectly promote the prostatic growth

and contractility of the prostate gland, and represent important risk factors for the development of symptomatic LUTS / BPH (Fig. 2). ATX-LPA axis, PPARγ signaling, hyperinsulinemia/IGF signaling and steroidal signaling are the emerging mechanisms which explains the association between dietary fat intake, obesity and BPH. However, further mechanistic as well as epidemiology based studies are required to delineate the role of lipids in the pathogenesis of BPH. Future research to investigate the direct effect of different types of FAs on the prostatic growth and isoforms specific characterization of insulin and IGF-IR signaling in response to dietary habit is warranted.

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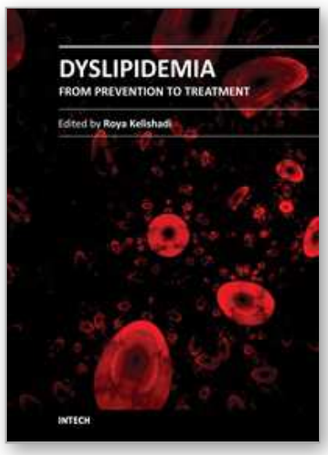


**Dyslipidemia - From Prevention to Treatment**
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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.



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