Benign prostatic hyperplasia (BPH) is a highly prevalent disease in the aged men population characterized by augmented cell proliferation and contractility of the prostate gland. Prior studies have demonstrated the relationship between BPH and insulin-resistance syndrome. During insulin-resistance, hyperinsulinemia develops to combat the decreased responsiveness of the body towards insulin. Although, the compensatory hyperinsulinemia prevents development of fasting hyperglycemia in insulin-resistant individuals, the increased level of circulating insulin directly and/or indirectly affects different molecular signaling and can promote prostatic growth. Insulin-resistance syndrome includes group of disorders, such as obesity, dyslipidemia, sympathetic overactivity, hyperinsulinemia and each individually reported as risk factor for the development of BPH. The present review describes the inter-relationships between different insulin-resistance associated factors and their possible involvement in the pathogenesis of BPH.

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**1. Introduction**

BPH is a disease of aged men population characterized by nonmalignant enlargement of the prostate gland (Berry et al., 1984). About 60% of men aged over 50 years have histological evidence of BPH and, after age 70, the proportion increases to 80% (Berry et al., 1984). Despite the high prevalence of BPH in aged men population, the disease pathogenesis is far from complete understanding. It is a chronic, progressive and highly prevalent disease, clinically manifests as lower urinary tract symptoms, posing socioeconomic burden to the patients. Today prostatic hyperplasia is the fourth most prevalent disease in men population aged over 50 years (Issa and Regan, 2007). BPH is rarely fatal, but if left untreated, serious life threatening complications, such as acute urinary retention may arise. Prostatic development and differentiation is affected by genetic (Sanda et al., 1994), nutritional (Bravi et al., 2006) and hormonal factors (Marker et al., 2003). Although, the etiology of BPH is not well understood, several theories have been proposed to explain the pathogenesis of BPH (Bosch, 1991; Srinivasan et al., 1995).
Testosterone–dihydrotestosterone signaling and mesenchymal–epithelial interactions are required for the normal prostatic growth and are known to play an important role in the progression of disease (Marker et al., 2003). Many risk factors for BPH such as insulin, insulin like growth factors (IGFs), and dyslipidemia might acts through androgen-independent mechanisms (Barnard and Aronson, 2009; Ikeda et al., 2000; Lucia and Lambert, 2008; Peehl et al., 1995; Vikram et al., 2010). Several experimental (Table 1) and clinical (Table 2) reports indicate the critical role of obesity and insulin-resistance associated complications in the pathogenesis of BPH (Hammarsten et al., 1998, 2009; Hammarsten and Hogstedt, 2001; Nandeesha et al., 2006; Parsons et al., 2006), Increased incidence of BPH in insulin-resistant and diabetic population (Issa and Hogstedt, 2001; Nandeesha et al., 2006; Parsons et al., 2006). Increased incidence of BPH in insulin-resistant and diabetic population (Issa and Hogstedt, 2001; Nandeesha et al., 2006; Parsons et al., 2006).

### Table 1
Experimental studies in different animal models showing effect of investigative strategies on the metabolic profile and subsequent effect on the parameters related to BPH.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Animal model</th>
<th>Strategy employed</th>
<th>Critical changes in the parameters</th>
<th>Effect on prostate gland</th>
<th>Primary factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sprague-Dawley rats</td>
<td>High-fat diet feeding</td>
<td>Increase in the body weight, insulin resistance, glucose level and insulin level</td>
<td>Prostatic enlargement and enhanced contractility</td>
<td>Insulin</td>
<td>Vikram et al. (2010)</td>
</tr>
<tr>
<td>2</td>
<td>Sprague-Dawley rats</td>
<td>High-fat diet feeding</td>
<td>Increase in the body weight, no change in the androgen axis and androgen response genes</td>
<td>Prostatic enlargement</td>
<td>Androgen independent</td>
<td>Cai et al. (2001)</td>
</tr>
<tr>
<td>3</td>
<td>Sprague-Dawley rats</td>
<td>Streptozotocin treatment</td>
<td>Decrease in the body weight, insulin and testosterone level</td>
<td>Decrease in the body weight, insulin and testosterone level</td>
<td>Smaller prostate</td>
<td>Vikram et al. (2008)</td>
</tr>
<tr>
<td>4</td>
<td>Sprague-Dawley rats</td>
<td>Streptozotocin treatment</td>
<td>Decrease in the body weight, insulin and testosterone level</td>
<td></td>
<td>Smaller prostate</td>
<td>Ikeda et al. (2000)</td>
</tr>
<tr>
<td>5</td>
<td>Bio Breeding rats (diabetes-prone and diabetes-resistant)</td>
<td>Genetically diabetic rats with or without streptozotocin treatment</td>
<td>Slight decrease in the body weight and plasma insulin level in genetically diabetic rats</td>
<td>Decrease in the body weight and plasma insulin level in STZ treated rats</td>
<td>Smaller prostate only in STZ treated rats</td>
<td>(Yono et al., 2005, 2008)</td>
</tr>
<tr>
<td>6</td>
<td>Brown Norvey rat</td>
<td>Natural aging process</td>
<td>Decrease in the testosterone level</td>
<td>Slight increase in the dorsal and lateral lobe of the prostate gland</td>
<td>Testosterone</td>
<td>Banerjee et al. (1998)</td>
</tr>
<tr>
<td>7</td>
<td>Wistar rats</td>
<td>Botulinum neurotoxin (type A) injection</td>
<td>Botulinum toxin type A inhibits fusion of neurotransmitter-containing synaptic vesicle with the neuronal membrane—Decreased sympathetic activity in prostates</td>
<td>Smaller prostate</td>
<td>Sympathetic activity</td>
<td>Silva et al. (2009)</td>
</tr>
<tr>
<td>8</td>
<td>Sprague-Dawley rats</td>
<td>Botulinum neurotoxin (type A) injection</td>
<td>Botulinum toxin type A inhibits fusion of neurotransmitter-containing synaptic vesicle with the neuronal membrane—Decreased sympathetic activity in prostates</td>
<td>Smaller prostate</td>
<td>Sympathetic activity</td>
<td>Dogweiler et al. (1998)</td>
</tr>
<tr>
<td>9</td>
<td>Spontaneously hypertensive rats</td>
<td>Susceptible to develop hypertension</td>
<td>Increase in the sympathetic activity</td>
<td>Prostatic hyperplasia (histological evidence)</td>
<td>Prostatic hyperplasia (histological evidence)</td>
<td>(Golomb et al., 2000; Matiyohu et al., 2003)</td>
</tr>
<tr>
<td>10</td>
<td>Wistar rats</td>
<td>Phenylephrine treatment</td>
<td>Decrease in the body weight</td>
<td>Prostatic hyperplasia (histological evidence)</td>
<td>Prostatic hyperplasia (histological evidence)</td>
<td>Golomb et al. (1998)</td>
</tr>
<tr>
<td>11</td>
<td>Sprague-Dawley rats</td>
<td>Denervation</td>
<td>Decrease in the sympathetic activity</td>
<td>Smaller prostate</td>
<td>Autoonomic nervous system activity</td>
<td>McVary et al. (2005)</td>
</tr>
<tr>
<td>12</td>
<td>Sprague-Dawley rats</td>
<td>High-fat diet feeding</td>
<td>Increase in the body weight and lipid level</td>
<td>Prostatic enlargement enhanced</td>
<td>Prostatic enlargement</td>
<td>Rahman et al. (2007)</td>
</tr>
<tr>
<td>13</td>
<td>Wistar rats</td>
<td>High-fat diet feeding</td>
<td>Increase in the body weight, lipid level and expression of peroxysome-proliferator-activated receptor-γ (PPARY) and androgen receptor</td>
<td>Saturated dietary fatty acids</td>
<td>Decreased parasympathetic supply</td>
<td>Eskobar et al. (2009)</td>
</tr>
<tr>
<td>14</td>
<td>Spontaneously hypertensive rats</td>
<td>Truncation of bilateral branches of parasympathetic pelvic nerve of major pelvic ganglion</td>
<td>No parasympathetic supply to the prostate gland</td>
<td>Prostatic atrophy</td>
<td>Decreased parasympathetic supply</td>
<td>Cai et al. (2008)</td>
</tr>
</tbody>
</table>

### Table 2
Clinical/epidemiological studies showing metabolic profile and parameters related to the BPH.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Effect on different parameters</th>
<th>Effect on prostate gland</th>
<th>Primary factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Insulin resistance, hyperinsulinemia and hyperlipidemia</td>
<td>Prostatic hyperplasia</td>
<td>Insulin</td>
<td>Nandeesha et al. (2006)</td>
</tr>
<tr>
<td>2</td>
<td>Insulin resistance, hyperinsulinemia, increased fasting glucose level and hyperlipidemia</td>
<td>Prostatic hyperplasia</td>
<td>Insulin</td>
<td>Ozden et al. (2007)</td>
</tr>
<tr>
<td>3</td>
<td>Increase in body weight, hyperinsulinemia hypertension, obesity increased fasting glucose level and low HDL-cholesterol level</td>
<td>Increased growth rates of prostate gland</td>
<td>Insulin, body mass index, hypertension, low HDL-cholesterol, NIDDM</td>
<td>Hammarsten and Hogstedt (1999)</td>
</tr>
<tr>
<td>4</td>
<td>Increase in body weight and fasting glucose level</td>
<td>Prostatic hyperplasia</td>
<td>Body mass index</td>
<td>Parsons et al. (2006)</td>
</tr>
<tr>
<td>5</td>
<td>Increase in body weight and plasma insulin level</td>
<td>Prostatic hyperplasia</td>
<td>Waist-to-hip ratio and insulin</td>
<td>Dahl et al. (2002)</td>
</tr>
<tr>
<td>6</td>
<td>Sympathetic activation, heart disease, sedentary life style and b-blocker use</td>
<td>Prostatic hyperplasia</td>
<td>Sympathetic over-activation</td>
<td>Meigs et al. (2001)</td>
</tr>
<tr>
<td>7</td>
<td>Dyslipidemia, fasting hyperglycemia</td>
<td>Prostatic hyperplasia</td>
<td>Dyslipidemia</td>
<td>Parsons et al. (2008)</td>
</tr>
</tbody>
</table>

NIDDM: Non insulin dependent diabetes mellitus.
Regan, 2007; Sarma and Kellogg Parsons, 2009; Stamatiou et al., 2009) strengthens the relationship between these two pathological conditions and makes this an increasingly relevant problem.

The aim of the present review is to summarize the influence of inter-related insulin-resistance associated complications, including obesity, dyslipidemia, sympathetic overactivity and hyperinsulinemia in the pathogenesis of prostatic hyperplasia. Further, the review puts forward the hypothesis that the hyperinsulinemia secondary to the development of insulin-resistance is at least in part involved in the pathogenesis of BPH.

2. Insulin signaling: The cost of compensation

Insulin signaling initiates on its interaction with the receptor, and involves complex downstream signaling cascade. The signaling cascade of insulin branches into two main pathways; one is IRS/PI-3Kinase pathway, which is primarily concerned with the glucose uptake and metabolic effects, second is Raf/MEK/ERK pathway, which mediates growth-stimulating effects of the hormone. The Raf/MEK/ERK pathway interacts with IRS/PI-3Kinase pathway to control proliferation and differentiation of the cells (Tanguchi et al., 2006).

The metabolic and mitogenic effects of insulin are mediated through two different pathways. Pathologic changes in the insulin sensitivity, complemented with rise in the plasma insulin level raises several interesting questions; i) does insulin-resistance develop equally to both of the pathways; ii) if not, then which pathway of insulin signaling gets affected; iii) what are the possible complications? Under insulin-resistant condition, IRS/PI-3Kinase pathway is impaired, whereas, Raf/MEK/ERK pathway remains unaffected. The compensatory rise in the insulin level might result in the over-activation of Raf/MEK/ERK signaling, to which different organs might show differential response either in nature and/or degree. In vasculature, pathway specific insulin-resistance leads to the over-activation of Raf/MEK/ERK signaling and thereby increased expression of adhesion molecules, resulting in the increased risk for hypertension and atherosclerotic plaque (Kim et al., 2006; Montagnani et al., 2002).

In addition to the cardiovascular diseases, the role of insulin-resistance and associated hyperinsulinemia has been well established in the pathogenesis of poly cystic ovary disease (Ehrmann, 1999).

Although, recent experimental and epidemiological studies have provided convincing evidence for the involvement of insulin-resistance and hyperinsulinemia in the pathogenesis of BPH (Dahle et al., 2002; Escobar et al., 2009; Hammarsten and Hogstedt, 1999; Nandeesha, 2008; Ozden et al., 2007; Parsons et al., 2006; Rahman et al., 2007; Yono et al., 2008), the underlying molecular events are far from complete understanding.

3. Molecular mechanism of insulin-resistance

Insulin-resistance generally precedes type 2 diabetes by 10 to 20 years and dietary habit has been known to affect the insulin sensitivity (Riccardi et al., 2004). Diet rich in fat content leads to increase in the plasma free fatty acid level and the condition has been greatly implicated in the pathogenesis of insulin-resistance (Kovacs and Stumvoll, 2005). At molecular level, high plasma free fatty acid level results in the increased intracellular level of diacylglycerol, fatty acylCoA and glycerol ceramides causing increased serine/threonine phosphorylation and decreased tyrosine phosphorylation of IRS-1/IRS-2 (through activation of PKCζ, JNK, and IKKβ) and hence reduced activation of PI-3Kinase (Yu et al., 2002). The IRS/PI-3Kinase downstream signaling of insulin is involved in the translocation of the GLUT4 from cytoplasm to the cell membrane (Shulman, 2000).

Alternatively, increased free fatty acid causes inhibition of pyruvate dehydrogenase and phosphofructokinase, resulting in the accumulation of glucose-6-phosphate, which in turn inhibits hexokinase II. The series of events ultimately lead to decreased entry of glucose into the cells (Shulman, 2000).

4. Insulin-resistance syndrome and prostatic hyperplasia

Insulin-resistance is a condition in which normal level of insulin elicits subnormal response. It is a condition which is associated with 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 (reviewed by (Kasturi et al., 2006)). Some isolated reports oppose the view regarding the relationship between insulin-resistance with BPH (Gupta et al., 2006; Park et al., 2008). The insulin-resistance associated disorders have been greatly implicated in the pathogenesis of BPH.

4.1. Obesity (waist-to-hip ratio, body mass index, BMI)

The prevalence of obesity is increasing alarmingly all over the world due to sedentary life style (Catenacci et al., 2009). It has been implicated in the etiology of BPH due to its influence on the metabolic and endocrine changes. Recent findings indicate that obesity substantially increases the risk for BPH (Dahle et al., 2002; Parsons et al., 2006, 2009). Health professionals follow-up study, prostate cancer prevention trial and a case control study of Italian men showed a positive association between obesity and BPH (Dahle et al., 2002; Giovannucci et al., 1994; Kristal et al., 2007; Zucchini et al., 2005). In a recent multicenter, cross-sectional, prospective study it was reported that the central obesity rather overall obesity is a better predictor of lower urinary tract symptoms (Lee et al., 2009). Fasting serum level of insulin in the patients with higher waist-to-hip ratio was found to be significantly high, indicating the involvement of insulin in the progression of disease (Dahle et al., 2002). Several independent studies have further supported the association between obesity and hyperinsulinemia (Becker et al., 2009; Koga et al., 2008; Vogeser et al., 2009). In contrast to this, few reports argue that, obesity is associated with increased estrogen-to-androgen ratio and sympathetic activity, both individually hypothesized to promote the development of prostatic hyperplasia (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-to-androgen ratio. Further mechanistic studies investigating the effect of obesity on the prostatic growth and its influence on androgen and insulin signaling in the prostate gland can shed light on the pathogenesis of BPH.

4.2. Dyslipidemia

Disturbance in the glucose and lipid metabolism is an integral part of insulin-resistance syndrome (Cohn et al., 2001; Fryan, 1993). Presence of BPH with hyperlipidemia is a frequently noted condition under clinical setup, and decreased level of HDL-cholesterol shows association with the enlargement of prostate gland. Recently it has been reported that the higher serum LDL is associated with greater risk of BPH (Parsons et al., 2008). Hyperlipidemia might be one of the important risk factors in the pathogenesis of BPH (Li et al., 2005b). Experimental studies indicate enlargement of prostate gland in the hyperlipidemic rats (Rahman et al., 2007; Vikram et al., 2010). In addition to the animal studies, epidemiological findings also support the relationship between dyslipidemia and prostatic hyperplasia (Nandeesha et al., 2006). In agreement with the previous study, Escobar et al. (2009), reported prostatic growth-promoting effects of dietary fatty acids, indicating the involvement of peroxysome-proliferator-activated receptor-gamma as a link between diet and augmented prostatic growth. However, the precise role and relative influence of hyperlipidemia and hyperinsulinemia in the pathogenesis of BPH is not clear.
4.3. Hypertension and sympathetic overactivity

Epidemiological findings have revealed association between sympathetic overactivity and lower urinary tract symptoms (McVary et al., 2005). Sympathetic overactivity is a key factor in the pathophysiology of hypertension (Palatini, 2001; Ward et al., 1996) and hypertensive men are more likely to undergo surgical intervention for irritative voiding symptoms often associated with BPH (Yang and Zhao, 2007). Thor et al. (2006) reported sympathetic overactivity in BPH patients. Patients with BPH and lower urinary tract symptoms are found to be at higher risk of cardiovascular diseases than general age matched population (Karatas et al., in press). In experimental studies, spontaneous hyperplasia has been observed in the aging genetically hypertensive rats which are known to have higher sympathetic tone (Golomb et al., 2000). Glandular injection of botulinum neurotoxin (type A), known to inhibit the release of neurotransmitters, causes atrophy of the prostate gland in the rat, underlines the critical role of autonomic nervous system in prostatic growth (Doggweiler et al., 1998; Silva et al., 2009). Enhanced contractility of prostate isolated from high-fat diet-fed rats (Vikram et al., 2010) can be attributed to the increased sensitivity of the tissue, as increased expression of alpha-adrenoceptor has been observed in the prostate of hyperlipidemic rats (Rahman et al., 2007). However, the status of insulin-resistance, insulin level, and sympathetic activity has not been examined, making it difficult to correlate insulin-resistance associated complications with the prostatic enlargement.

4.4. Hyperinsulinemia

To combat the decreased responsiveness of insulin-sensitive tissues towards insulin, β-cells secrete more amount of insulin and hence hyperinsulinemia is observed. The development of hyperglycemia in insulin-resistant individuals is prevented by compensatory rise in the insulin level, which is known to have growth-stimulating effects (McKeehan et al., 1984). Augmented prostatic epithelial cell proliferation in insulin-resistant rats can be attributed to the growth-stimulating effect of insulin (Vikram et al., 2010). Montagnani et al. (2002), reported that inhibition of PI3-Kinase with concomitant increase in the insulin concentration (mimicking the typical insulin-resistance associated compensatory hyperinsulinemic condition) leads to enhanced mitogenic effects in the endothelial cells in vitro. Further, Morales et al., reported involvement of the Raf/MEK/ERK signaling in the growth of prostate gland in rodents (Morales and Badran, 2003). Experimental hypoinsulinemia induced by selective β-cell toxin (streptozotocin) leads to dramatic decrease in the size of prostate gland (Ikeda et al., 2000; Vikram et al., 2008). However, genetically diabetic rats with similar degree of hyperglycemia demonstrate little effect on the size of prostate gland (Yono et al., 2005, 2008). Epidemiological findings also acknowledge insulin-resistance and hyperinsulinemia as an independent risk factor for prostatic hyperplasia (Hammarsten et al., 2009; Hammarsten and Hogstedt, 2001; Nandeesha et al., 2006). Based upon experimental and epidemiological evidence hyperinsulinemia is substantially associated with the increased risk for BPH. Mechanistic investigations employing transgenic animal models which are known to develop hyperinsulinemia and obesity spontaneously with the progression of age and prostate-specific insulin receptor knockout animal, can help to understand the role of insulin in the pathogenesis of BPH.

5. Influence of insulin like growth factor on the prostatic growth under hyperinsulinemic condition

Hyperinsulinemic condition increases free insulin like growth factor-1 in serum (Nam et al., 1997) and has been known to be associated with higher risk of BPH (Chokkalingam et al., 2002). Herbal products, such as lycopene, saw-palmitto extract which are known to inhibit the insulin like growth factor-1 signaling are found to have growth-inhibiting effect on the prostate (Wadsworth et al., 2004; Wertz et al., 2004). Insulin like growth factors are reported to bind to the insulin receptor and to mediate metabolic as well as mitogenic signaling of insulin (Belfiore and Frasca, 2008; Li et al., 2005a). Insulin receptor exhibits high degree of similarity with insulin like growth factor receptor (Ulrich et al., 1986) and insulin like growth factors shows resemblance with the proinsulin (Cohick and Clemmons, 1993). This raises the possibility of the binding of insulin to the insulin like growth factor receptor (type-1) under hyperinsulinemic condition.

6. Influence of steroidal hormones on the prostatic growth under hyperinsulinemic condition

Androgens are required for the normal growth and development of the prostate and have been implicated in the pathogenesis of BPH (Markier et al., 2002). About 50% of the testosterone present in the serum is bound to the sex-hormone binding globulin. Only free testosterone can enter into prostatic cells and gets converted to the dihydrotestosterone by 5-alpha reductase enzyme. A recent report presented at the society for the study of reproduction has indicated increased expression of 5-alpha reductase (type-1) in the ovarian granulosa cells (Kayampilly et al., 2009). Further, it has been reported that insulin/IGF-1 signaling activates androgen signaling through direct interaction of Faso 1 with androgen receptor (Fan et al., 2007). These reports point towards the possibility of the increased expression of 5-alpha reductase and augmented androgen signaling in the prostate gland under hyperinsulinemic condition, which might contribute to the prostatic enlargement. However, it remains to be experimentally verified. Men undergone sex-reversal and castrated animals demonstrate atrophy of the prostate gland (de Voogt et al., 1987; Shabsigh et al., 1998). Further, no difference in the size of prostate gland isolated from normal or insulin-resistant rats undergone castration suggests the role of testosterone in the prostatic growth (unpublished data). Collectively, it appears that, hyperinsulinemia can promote prostatic growth without affecting the plasma testosterone level but its presence is essential. Investigations on the 5-alpha reductase enzyme expression and testosterone-dihydrotestosterone axis in the prostate gland under hyperinsulinemic condition may be useful to better understand the pathogenesis of the disease.

7. Insulin-resistance in rats: Does it affect prostatic growth

Several epidemiological reports indicate insulin-resistance, obesity, dyslipidemia and hyperinsulinemia as a risk factor for BPH (Nandeesha et al., 2008; Nandeesha et al., 2006; Parsons et al., 2006, 2008). The thought to verify these effects in experimental animals is very obvious and can provide an animal model for BPH, which fits to the observed epidemiological findings. To our surprise, induction of insulin-resistance in Sprague–Dawley rats by high-fat diet feeding has led to the increased cell proliferation, enhanced alpha-adrenoceptor mediated contractility and enlargement of the prostate gland. Further, mechanistic evaluation revealed enhanced Raf/MEK/ERK branch of insulin signaling in the prostate of insulin-resistant rats (Vikram et al., 2010). Other laboratories have also reported enlargement of ventral prostate in rats kept on diet rich in fat (Cai et al., 2001; Escobar et al., 2009; Rahman et al., 2007). In contrast to the high-fat diet-fed rats, several hormonal and non-hormonal approaches for inducing BPH in rodents require administration of the exogenous materials (Engelstein et al., 1996; Noa et al., 2005; Servadio et al., 1986; Thiyagarajan et al., 2002). Considering the etiopathogenesis of human BPH, the high-fat diet-fed rats may provide a particularly advantageous experimental model for BPH.
8. Conclusions

Insulin-resistance syndrome is associated with the group of disorders which includes, obesity, glucose intolerance, endothelial dysfunction, dyslipidemia, diabetes and hypertension. Careful review of the experimental and clinical/epidemiological literature pertaining to the co-existence of insulin-resistance or insulin-resistance associated factors and BPH, clearly shows that insulin-resistance is an important risk factor for prostatic hyperplasia. Further, different components of the insulin-resistance syndrome are interlinked with each other and activate several prostatic growth-promoting mechanisms (please see Fig. 1) and thereby affect the subsequent susceptibility for developing symptomatic BPH.

Future research to investigate the effect of insulin-resistance on the insulin like growth factor and testosterone–dihydrotestosterone axis could facilitate the understanding of the mechanisms responsible for increased incidence of BPH in insulin-resistant individuals. Further, evaluation of herbal products with potential of (i) inhibiting insulin/IGF-1 signaling in the prostate gland or (ii) improving glucose disposal to normalize hyperinsulinemia secondary to the insulin-

![Fig. 1. Inter-relationships between different insulin-resistance associated factors and their possible involvement in the pathogenesis of prostatic enlargement. Impairment in the insulin signaling in classical insulin-sensitive tissues (muscle, liver and adipose tissue) promotes development of hyperglycemia, dyslipidemia and hyperinsulinemia. The increased level of insulin is sensed by the ventromedial hypothalamus and results in the sympathetic overactivity. The inter-related insulin-resistance associated factors promote prostatic growth through modulation of the insulin, insulin like growth factor-1, PPAR-α/γ and androgen signaling. G-6-P: Glucose-6-phosphate, GLUT2 and GLUT4; Glucose transporter 2 and 4, HK; Hexokinase, PFK; Phosphofructokinase, PDH; pyruvate dehydrogenase, PPAR-α/γ; peroxysome-proliferator-activated receptor alpha/gamma, IGFBP; Insulin like growth factor binding protein, SHBG; Sex-hormone binding globulin, GH; growth hormone, 5-AR; 5-alpha reductase, T; Testosterone, DHT; Dihydrotestosterone, AR; Androgen receptor.](image-url)
resistance might be useful objectives for their potential use in the treatment of BPH.

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References


Benign prostatic hyperplasia (BPH) is a highly prevalent disease in the aged men population characterized by augmented cell proliferation and contractility of the prostate gland. Prior studies have demonstrated the relationship between BPH and insulin-resistance syndrome. During insulin-resistance, hyperinsulinemia develops to combat the decreased responsiveness of the body towards insulin. Although, the compensatory hyperinsulinemia prevents development of fasting hyperglycemia in insulin-resistant individuals, the increased level of circulating insulin directly and/or indirectly affects different molecular signaling and can promote prostatic growth. Insulin-resistance syndrome includes group of disorders, such as obesity, dyslipidemia, sympathetic overactivity, hyperinsulinemia and each individually reported as risk factor for the development of BPH. The present review describes the inter-relationships between different insulin-resistance associated factors and their possible involvement in the pathogenesis of BPH.

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Reader Comments
Written by aerie1022@sbcglobal.net on 2010-08-23 16:33:58

This is very interesting in light of the insulin resistance that develops in hypogonadism (low testosterone)
Beyond the Abstract - Insulin-resistance and benign prostatic hyperplasia: The connection, by Ajit Vikram, M.S. (Pharm.) and Gopabandhu Jena, Ph.D.

Friday, 01 October 2010

BERKELEY, CA (UroToday.com) - Insulin-resistance is currently an increasing worldwide concern. Increased incidence of benign prostatic hyperplasia in the insulin-resistant and diabetic population strengthens the relationship between these two pathological conditions. During insulin-resistance, hyperinsulinemia develops to combat decreased responsiveness of the body towards insulin. Recent experimental and clinical research indicates that insulin plays an important role in the prostatic enlargement, and hyperinsulinemia appears to be the most appropriate explanation for the association between insulin-resistance and benign prostatic hyperplasia.

The present findings may attract the attention of urologists because, for the first time, we provide mechanistic evidence of how insulin-resistance and associated disorders such as obesity, dyslipidemia, sympathetic over activity and hyperinsulinemia together can promote the prostatic growth. Lifestyle and dietary habits have been known to be associated with the development and progression of prostatic hyperplasia. Simple experiments utilizing hypoinsulinemic (streptozotocin-treated) and hyperinsulinemic (high-fat diet) rats clearly demonstrates that, apart from age, chronic change in the systemic insulin level affects the growth of the prostate gland (Figure 1). Insulin-resistance associated secondary rise in insulin can stimulate prostatic growth through:

i. insulin-receptor mediated growth promoting effects and/or
ii. by augmenting the insulin like growth factor-1 receptor signaling.

Recently, it has been reported that insulin/insulin like growth factor signaling activates androgen signaling through direct interaction of the Foxo-1 with the androgen receptor. The hyperinsulinemia can also affect prostatic growth by affecting the androgen signaling in the prostate gland, which may involve,

i. increase in the androgen synthesis,
ii. decrease in the expression of sex-hormone binding globulin, and
iii. decrease in the inhibition of androgen signaling through direct interaction of Foxo-1 with the androgen receptor.

Further, insulin can increase the conversion of testosterone into dihydrotestosterone, which has long been acknowledged as the major controller of prostatic growth. Based on the experimental
and epidemiological evidences, hyperinsulinemia can play a crucial role in prostatic enlargement. However, mechanistic investigations employing transgenic animal models which are known to develop hyperinsulinemia and obesity spontaneously with the progression of age, and the prostate-specific insulin receptor knockout animal can help to better understand the role of insulin in the pathogenesis of benign prostatic hyperplasia.

The compensatory hyperinsulinemia might result in the over-activation of insulin signaling, to which different organs might show differential response either in nature and/or degree. In vasculature, over-activation of insulin signaling results in the increased expression of the adhesion molecules, resulting in the higher risk for hypertension and atherosclerotic plaque.[15, 16] In females, the role of insulin-resistance and associated hyperinsulinemia has been well established in the pathogenesis of polycystic ovary syndrome (PCOS).[17] Insulin-sensitizing drugs such as metformin and pioglitazone are reported to have a beneficial effect in the treatment of PCOS.[18-20] Although, alopecia and glucose metabolic disorder has been put forwarded as male equivalent for the PCOS,[21] prostatic enlargement may be another one. These arguments favor the idea that research on insulin-sensitizers can pave the way to identifying a novel therapeutic strategy for the management of prostatic enlargement in insulin-resistant individuals.

(Figure 1) Effect of age and insulin on the weight of the prostate in rats. Dietary manipulation (Normal pellet diet (NPD) or high-fat diet (HFD) feeding) and streptozotocin (STZ) treatment was introduced at the age of nine weeks. At the end of the study, HFD feeding led to increase in the insulin level (≈ 250 %) and prostate weight (≈ 30 %), while STZ treatment led to decrease in the insulin level (≈ 80 %) and prostate weight (≈ 90 %). This indicates the role of insulin in the prostatic growth.
References:


Written by:
Ajit Vikram, M. S. (Pharm.) and Gopabandhu Jena, Ph. D. as part of Beyond the Abstract on UroToday.com. This initiative offers a method of publishing for the professional urology community. Authors are given an opportunity to expand on the circumstances, limitations etc... of their research by referencing the published abstract.

Insulin-resistance and benign prostatic hyperplasia: The connection - Abstract
Insulin-Resistant Diabetes and Benign Prostatic Hyperplasia: The Connection

04 Nov 2010

Insulin-resistance is currently an increasing worldwide concern. Increased incidence of benign prostatic hyperplasia in the insulin-resistant and diabetic population strengthens the relationship between these two pathological conditions. During insulin-resistance, hyperinsulinemia develops to combat decreased responsiveness of the body towards insulin. Recent experimental and clinical research indicates that insulin plays an important role in the prostatic enlargement, and hyperinsulinemia appears to be the most appropriate explanation for the association between insulin-resistance and benign prostatic hyperplasia.

The present findings may attract the attention of urologists because, for the first time, we provide mechanistic evidence of how insulin-resistance and associated disorders such as obesity, dyslipidemia, sympathetic over-activity and hyperinsulinemia together can promote the prostatic growth. Lifestyle and dietary habits have been known to be associated with the development and progression of prostatic hyperplasia. Simple experiments utilizing hypoinsulinemic (streptozotocin-treated) and hyperinsulinemic (high-fat diet) rats clearly demonstrates that, apart from age, chronic change in the systemic insulin level affects the growth of the prostate gland.

Insulin-resistance associated secondary rise in insulin can stimulate prostatic growth through:

i) insulin-receptor mediated growth promoting effects and/or

ii) by augmenting the insulin-like growth factor-1 receptor signaling.

Recently, it has been reported that insulin/insulin-like growth factor signaling activates androgen signaling through direct interaction of the Foxo-1 with the androgen receptor. The hyperinsulinemia can also affect prostatic growth by affecting the androgen signaling in the prostate gland, which may involve:

i) increase in the androgen synthesis,

ii) decrease in the expression of sex-hormone binding globulin, and

iii) decrease in the inhibition of androgen signaling through direct interaction of Foxo-1 with the androgen receptor.

Further, insulin can increase the conversion of testosterone into dihydrotestosterone, which has long been acknowledged as the major controller of prostatic growth. Based on the experimental and epidemiological evidences, hyperinsulinemia can play a crucial role in prostatic enlargement. However, mechanistic investigations employing transgenic animal models which are known to develop hyperinsulinemia and obesity spontaneously with the progression of age, and the prostate-specific insulin receptor knockout animal can help to better understand the role of insulin in the pathogenesis of benign prostatic hyperplasia.

The compensatory hyperinsulinemia might result in the over-activation of insulin signaling, to which different organs might show differential response either in nature and/or degree. In vasculature, over-activation of insulin signaling results in the increased expression of the adhesion molecules, resulting in the higher risk for hypertension and atherosclerotic plaque. In females, the role of insulin-resistance and associated hyperinsulinemia has been well established in the pathogenesis of polycystic ovary syndrome (PCOS). Insulin-sensitizing drugs such as metformin and pioglitazone are reported to have a beneficial effect in the treatment of PCOS. Although, alopecia and glucose metabolic disorder has been put forward as male equivalent for the PCOS, prostatic enlargement may be another one. These arguments favor the idea that research on insulin-sensitizers can pave the way to identifying a novel therapeutic strategy for the management of prostatic enlargement in insulin-resistant individuals.
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Main News Category: Urology / Nephrology

Also Appears In: Diabetes,
Insulin-Resistance and Benign Prostatic Hyperplasia: The Connection

Insulin-resistance is currently an increasing worldwide concern.[1, 2]. Increased incidence of benign prostatic hyperplasia in the insulin-resistant and diabetic population strengthens the relationship between these two pathological conditions [3-8]. During insulin-resistance, hyperinsulinemia develops to combat decreased responsiveness of the body towards insulin. Recent experimental and clinical research indicates that insulin plays an important role in the prostatic enlargement, and hyperinsulinemia appears to be the most appropriate explanation for the association between insulin-resistance and benign prostatic hyperplasia [8].

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Insulin-Resistance and Benign Prostatic Hyperplasia

Research on insulin-sensitizers can pave the way to identifying a novel therapeutic strategy for the management of prostatic enlargement in insulin-resistant individuals....

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Insulin-resistance may increase chances of benign prostatic hyperplasia

Posted on 23 August 2010

The Department of Pharmacology and Toxicology and the National Institute of Pharmaceutical Education and Research have recently conducted a study on the connection between insulin-resistance and benign prostatic hyperplasia. Because of its high prevalence in men over the age of 40, BPH has been under-going a series of studies in order to understand why, exactly, so many men experience its symptoms. Several theories have been offered as to why the prostate grows or swells to the point of blocking the urethra. These theories include one dealing with the hormones testosterone and estrogen and one focusing on dihydrotestosterone (DHT). DHT may accumulate in high levels as men age, which may encourage the growth of cells. Further, benign prostatic hyperplasia may occur because prostate gland cells are given instructions to grow or become more sensitive to growth hormones later in life.

But the researchers at the Department of Pharmacology and Toxicology have focused on BPH in insulin-resistant patients. They explain that during the progression of insulin-resistance, the condition hyperinsulinemia first develops to prevent a decrease in responsiveness of the body towards insulin. As a result, an increase of circulating insulin occurs in the body, which affects molecular signaling and may even lead to the growth of the prostate gland. Once the prostate gland growth has been initiated, patients may experience the symptoms associated with benign prostatic hyperplasia including a blocked urethra, frequent, urgent need to urinate, reduced urine flow, and nightly trips to the bathroom.

Hyperinsulinemia must not be confused with diabetes or hypoglycaemia; these are separate conditions. But if left unmonitored, hyperinsulinemia may develop into diabetes. Among the insulin-resistant conditions tested at the Institute are obesity, dyslipidemia, and sympathetic over-activity of insulin. The study reports a connection between all of these conditions and prostate enlargement and, thus, the development of benign prostatic hyperplasia.