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Diabetes & its Complications

Parallels between Insulin Resistance and Testosterone Resistance: Another Facet of the Metabolic Syndrome? - Syndrome Y

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ABSTRACT

Insulin resistance in type 2 diabetes is a long-established fact and a target for therapeutic intervention. We present the case for there being similar resistance to testosterone causing a relative deficiency in the majority of cases of clinical onset of symptoms of deficiency of this hormone in the adult or comorbid conditions, especially metabolic syndrome. There are many parallels between resistances to the two hormones. This is seen in aetiology, age of onset, genetics, ethnicity, heredity, familial influences, association with obesity, links with viral diseases, and autoimmune conditions. Like diabetes, androgen deficiency can arise before birth, in early life, resulting in early onset, or later on leading to adult onset, with resistance playing a greater role. Similarly treatments such as weight loss and exercise have the effect of reducing resistance to both hormones. Clinical observations suggest that the duration of action of a standard dose of either pellet implants of testosterone, or an injection of testosterone undecanoate, might be a suitable measure of resistance to this hormone. Because of similar causation and co-existence of resistance to these two hormones in metabolic syndrome it is suggested that this may be new facet of the condition which because of its association with the male chromosome could be re-named as Syndrome-Y.

Keywords

Metabolic syndrome, Type 1 and Type 2 diabetes, Testosterone deficiency.

Introduction

Since it was first described by Harold Himsworth in 1939 [1], insulin resistance has been recognized as the main contributory factor to Type 2 diabetes. What is less well acknowledged is that resistance to the action of androgens is likely to be a major factor in adult onset testosterone deficiency [2], and that there are overlapping factors in the two conditions. Because of the importance of this concept in the diagnosis and treatment of both diabetes and testosterone deficiency syndrome (TDS) it was considered important to emphasise the many parallels between both Type 1 and Type 2 diabetes and early and late onset androgen deficiency.

Diagnosis of Androgen Deficiency

There are currently two approaches to the diagnosis of testosterone deficiency:

Current Laboratory-Centred View

Current guidelines base the diagnosis on total testosterone (TT) and/or free testosterone usually measured as calculated free testosterone (CFT), below 'threshold' values, together with symptoms which variable in intensity and range. Unfortunately, in clinical practice it has been repeatedly found that there is no relationship between TT, CFT or other laboratory measure of androgens and the clinical diagnosis or the effectiveness of treatment [3-5].

This was most clearly shown in a recent study of over 2,500 men with symptoms of androgen deficiency treated using 7 different preparations over a 25 year period in the UK Androgen Study (UKAS) [6] (Figure 1).

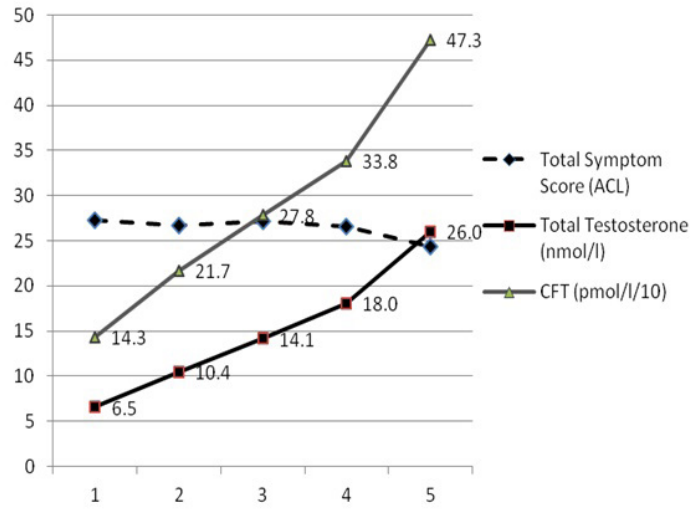


Figure 1: Dissociation between levels of either total testosterone (TT) or calculated free testosterone (cFT) and symptoms.

Also it was found that improvement of symptoms on treatment was the same for patients whose initial testosterone was above the commonly accepted threshold of 12nmol/l total testosterone and those below it (Figure 2).

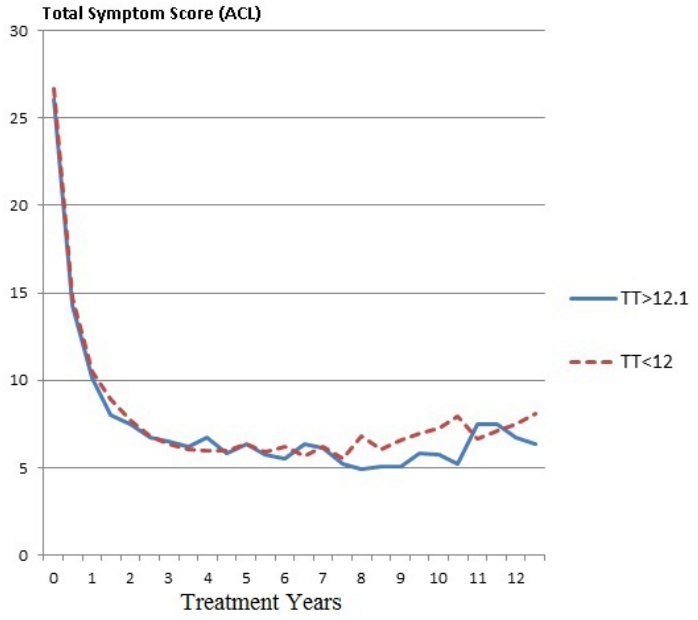


Figure 2: Total symptom scores (ACL) over 12 years for patients whose pre-treatment testosterone levels were above and below 12 nmol/l.

These findings would appear to argue for their being variable degrees of resistance to the action of testosterone causing dissociation of androgen levels and their clinical effects, leading to a re-consideration of symptoms as being the best diagnostic test for the resulting relative androgen deficiency. According to this patient-centred view it is the laboratory tests which are non-specific rather than the symptoms as often claimed.

Diabetes and testosterone deficiency

Up to 50% of diabetics are thought to be testosterone deficient [7], and both conditions are increasing as population's age and get more obese. It was therefore thought appropriate to look at common factors in their causation, pathology and clinical associations, and see if these might be considered different facets of the same condition, the metabolic syndrome, with similar factors causing resistance i,e. reduced biological action, to both insulin and testosterone.

Causes

Like diabetes, androgen deficiency can arise before birth, in early life, resulting in early onset, or later on leading to adult onset, with resistance playing a greater role.

Age

There are two key ages of onset of diabetes, the twenties for type one and the fifties for type 2. This parallels the age of onset of testosterone deficiency.

Hereditary Factors

Due to different aetiology, Type 2 diabetes has a stronger genetic link than Type 1. Whites with type 1 diabetes have genes called Human Leucocyte Antigen HLA-DR3 or HLA-DR4. The HLA-DR7 gene may put African Americans at risk, and the HLA-DR9 gene may put Japanese at risk.

Studies of monozygotic and dizygotic twins [40] have shown that familial factors accounted for twice as much of the concordance in TT and FT, and dihydrotestosterone (DHT) as genetic factors, and virtually all genetic differences in sex hormone binding globulin (SHBG) and aromatase activity. In all these factors, nurture appeared more important than nature.

Only in oestradiol and luteinizing hormone levels did heredity have a slightly greater influence. It is suggested that similar diet and physical activity levels in families may explain most of these factors in determining androgen levels, and hence, liability to androgen deficiency.

Best recognized as causing variable degrees of testosterone resistance are modifications of the CAG or GGN androgen receptors. Genetic mutations in the AR have been shown to affect genital development, prostate tissue, spermatogenesis, bone density, hair growth, cardiovascular risk factors, psychological factors, insulin sensitivity, TT, SHBG, and FT levels.

CAG (Polyglutamine) Variations

CAG repeat lengths vary normally between 18 and 24 the greater the length, the more the androgen resistance, and in extreme cases, complete androgen insensitivity can cause loss of male phenotype in the androgen insensitivity syndrome. Longer mutations can also arise in prostate cancer, especially when it is metastatic or becomes hormone resistant [8].

Asian races with 22–23 CAG repeats have lower TT, SHBG, and FT, with greater insulin resistance, more diabetes and less prostate cancer than Afro-Caribbeans, who have 18–20 repeats, higher TT,

SHBG, and FT, and half the insulin resistance but more prostate cancer. White Europeans with 21–22 are intermediate in all these factors.

Strong positive correlations have been found between CAG repeat lengths, TT, FT, and LH, and are attributed to differences in androgen sensitivity and feedback set point [9].

GGN (Polyglycine) Variations

It has been shown both in vivo and in vitro that small differences in the length of the GGN codon can have marked effects on the activity of the AR, particularly when combined with longer CAG repeat lengths.

A study of infertile men in Sweden showed that those with 24 GGN repeats had lower testicular volumes, decreased seminal prostate specific antigen (PSA) and zinc, compared with those with 23 repeats, and concluded that the former was associated with relative androgen resistance [10].

The same Scandinavian group also found that unlike normal males, boys with hypospadias more often have AR gene with 24 rather than 23 repeats [11]. Longer GGN repeat lengths can also be linked to androgen resistance and may be the cause of 'testicular dysgenesis syndrome' which includes testicular maldescent, hypospadias, testicular cancer, and infertility. This is sometimes summarized as “a bad testis” and attributed to the greater sensitivity of this genome to adverse environmental influences, ranging from maternal smoking to organochloride pollutants. It is more common in mothers with mild gestational diabetes [12].

It has been shown in vitro that ARs with other glutamine numbers than 23 have lower transactivating capacity in response to both testosterone and DHT, and it is suggested that these could be linked to congenital malformations and other signs of a lower AR activity [13].

In these ways, minor variations in the AR gene can have major consequences in deciding the structure and function of androgen-responsive tissues throughout life. Referring to the variations in the CAG repeats, Zitzmann and Nieschlag state that “this modulation of androgen effects may be small but continuously present during a man’s life- time and, hence, exerts effects that are measurable in many tissues as various degrees of androgenicity and represents a relevant effector of maleness” [14]. With the inclusion of variations in glycine residues, this leads to a theory of the overall genetic regulation of androgen action within a particular individual.

Type 2 diabetes is more than six times more common in people of South Asian descent and up to three times more common among people of African and African-Caribbean origin. In the UK studies show that people of Black and South Asian ethnicity also develop Type 2 diabetes on average 10 years earlier age than people from the white population.

Malay and Indian men have a higher disease burden compared to Chinese men and are more likely to suffer with ED, TDS and MetS. MetS, which are closely related to TDS and ED [15].

Obesity

Obesity is closely associated with type 2 diabetes, and avoiding and correcting this is one of the main goals of treatment .This is a proinflammatory state resulting in increased release and secretion of excess cytokines and adipokines, free fatty acids (FFA), and oestrogens from adipose tissue. These increases are important risk factors that may contribute to the development of metabolic syndrome [16], and type 2 diabetes as well as androgen deficiency.

Visceral fat is an active secretary tissue producing inflammatory cytokines, adipokines, biochemical modulators, and other proinflammatory factors including interleukin (IL)-6, IL-1b, plasminogen activator inhibitor-1, tumournecrosis factor (TNF)-α, angiotensinogen, vascular endothelial growth factor, and serum amyloid A (Figure 3).

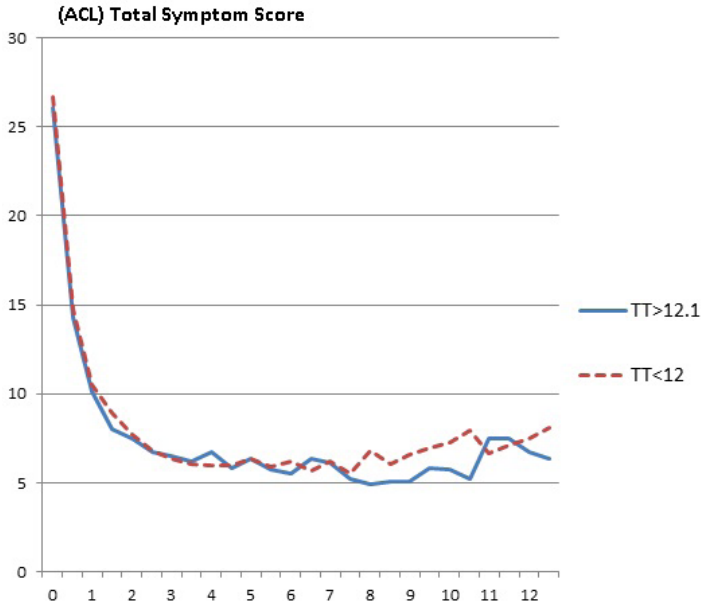


Figure 3: Total symptom scores (ACL) over 12 years for patients whose pre-treatment testosterone levels were above and below 12 nmol/l.

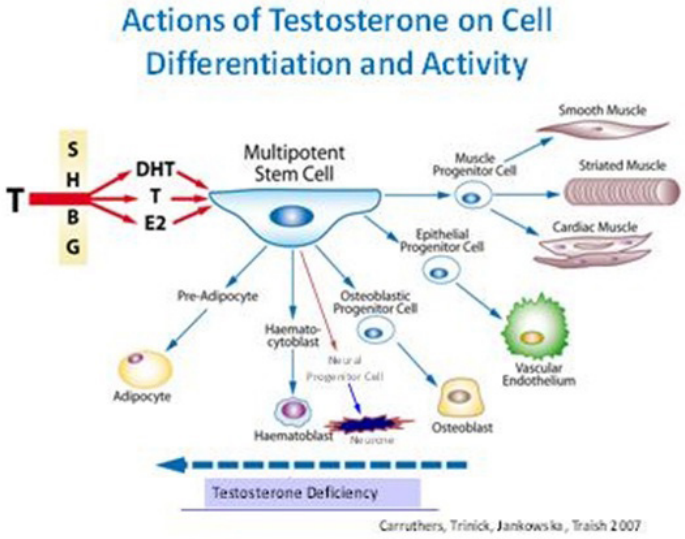
These factors contribute to systemic and peripheral vascular inflammation and dysfunction. One potential mechanism of how visceral adiposity and inflammatory response modulate insulin sensitivity involves the release of free fatty acids. FFA activates nuclear factor-kB pathways resulting in increased synthesis of TNF-α, probably in immune cells. This further activates lipolysis as well as increased synthesis of IL-6 and macrophage chemo-attractant protein-1, which increases recruitment of more macrophages and modulates insulin sensitivity. Increased production of TNF-α also enhances expression of adhesion molecules in both endothelium and vascular smooth muscle cells. IL-6 stimulates hepatic synthesis of C-reactive protein, a nonspecific marker of vascular inflammation.

In addition, TNF-α contributes to the dysregulation of insulin, modulation of endothelin-1-mediated vasoconstriction and nitric oxide–mediated vasodilation, hence promoting vasoconstriction. Release of adipokines facilitates monocyte adhesion and migration into the vessel wall as well as the conversion of monoctyes to macrophages.

Obesity and androgen deficiency

Aromatase, the enzyme that converts testosterone to estradiol, is found in adipose tissue, but is also present in the testis itself [16]. Obesity is associated with elevated oestrogen in men activating hypothalamic oestrogen receptors which trigger inhibition of the hypothalamic-pituitary gonadal axis. Treatment with aromatase inhibitors reverses the androgen deficiency associated with obesity [17].

Other studies indicate that interactions between low testosterone and visceral adiposity acting through proinflammatory agents (Figure 4) and result in insulin resistance an d vascular endothelial dysfunction, which are potential causal factors for increased CVD and ED [18].



In the European Male Aging Study, low serum [19] testosterone was more frequent in men with comorbidities such as obesity, metabolic syndrome, and type 2 diabetes. In studies from diabetes clinics, total, bioavailable, and free testosterone levels were low in men with type 2 diabetes [20].

Stress

Stress can contribute to the onset of both diabetes and androgen deficiency. Short term it causes the release of adrenaline, which increases blood glucose, and noradrenaline, which raises free fatty acids. Longer term it can raise cortisol levels which also increases blood glucose. These same stress related changes all oppose the production of testosterone and antagonise its action.

Alcohol

Alcohol is known to damage both the pancreas and testes. It contributes to diabetes in 3 ways. Firstly heavy drinking can reduce the body's sensitivity to insulin, which can trigger type 2 diabetes. Diabetes is a common side effect of chronic pancreatitis, which is mainly caused by heavy drinking. Thirdly, alcohol is very high in calories, contributing to obesity and the risk of developing type 2 diabetes.

Though excess alcohol intake is well recognized as a cause of infertility, its effects short and long-term effects on testosterone production are often overlooked.

Short-term, low dose alcohol intake has been found to increase testosterone levels in both women and men. Long term in men it has been found that moderate levels of stable alcohol intake (non-binge drinking) had no adverse effects on gonadal function, as estimated by testosterone levels and the free testosterone index [21].

In contrast, excess alcohol intake, short or long term, has a variety of adverse effects on androgen status in men. Acutely, high doses cause a decrease in androgen levels by a variety of mechanisms. Partly, these are related to a direct inhibition of testicular T production by acetaldehyde derived from the metabolism of alcohol [22]. Also alcohol suppresses LHRH release, by stimulating beta-endorphinergic neurons that inhibit the production of noradrenaline, which drives the nitric oxide mediated release of LHRH [23].

However, the majority of the endocrine effects of alcohol are probably indirect, resulting from either the stress of intoxication (stimulation of cortisol, catecholamines and possibly GH and prolactin), changes in the level of intermediary metabolites (e.g. a fall in circulating FFA stimulating GH secretion) or changes in the metabolism of hormones (e.g. catecholamines, oestrogens, androgens) resulting from alteration in intracellular redox state or tissue damage [24].

This is certainly the case in prolonged excess alcohol intake, where there is multi-organ damage, with a variety of adverse effects on androgen status. Depending on the duration and degree of the overdose, many of these persist, even when alcohol has been withdrawn, the liver function tests may have returned to normal. This is why in any testosterone deficient patient, it is important to take a history of previous as well as present alcohol consumption.

The long term effect of high doses of alcohol on increasing oestrogen production, and possibly greater intake of phyto-oestrogens in some forms of alcohol, especially beer, can affect androgen metabolism in two ways. Raised oestrogen levels, particularly as seen in cirrhosis with increased aromatisation in the greater adipose tissue stores and in the liver, both inhibits gonadotrophin release, and increases the production of SHBG. This combination of low testosterone and high SHBG further reduces the availability of free testosterone.

Infections

There is a two way relationship between diabetes and infections whether bacterial or viral, and infections can cause both types of diabetes. An accumulation of scientific research today suggests that

Type 1 diabetes is an autoimmune disease. Genetic predisposition and environmental factors (such as a viral infection) are thought to be co-factors in the development of autoimmune disease, including diabetes.

The emerging paradigm for Type 1 was formulated in 1974 as follows: 'one or more immune-response genes associated with HLA-A8 and/or W15 might be responsible for an altered T-lymphocyte response. The genetically determined host response could fail to eliminate an infecting virus (Coxsackie B4 and others) which in turn might destroy the pancreatic beta-cells or trigger an autoimmune reaction against the infected organ'.

Mumps is the classic example of an infection causing an endocrine disorder. The resultant orchitis, first described by Hippocrates, occurs in 25%-35% of post-pubertal cases, and like many testicular disorders, may affect its endocrine function as well as sperm production. It has also been implicated with Type 1 diabetes as has rubella.

This potential for testicular damage to be caused by a wide variety of viruses may be linked to damage to the immunological defense system of the testes, which is only established at puberty. The testis has unique 'immune privilege' in three ways. Firstly, diploid spermatogonia in the infant testis begin to divide and differentiate into haploid spermatozoa at puberty, causing the production of so-called 'novel antigens'. At the same time adjacent Sertoli cells form complex net-works of tight junctions that cause isolation of the tubular contents from the blood vascular compartment. This 'blood-testis barrier' seals off the spermatogenic and testosterone producing Leydig cells from the body's immunological defence mechanism, and largely prevents the production of auto-antibodies to them.

What auto-antibodies do arise seem to be dealt with by two other mechanisms regulating immune function within the testis. The endothelial cells of the testicular microvasculature which develops at puberty under androgenic stimulation, selectively limit the diffusion of antigenic material into the circulation. Also, Leydig cells are able to adhere to lymphocytes and suppress their proliferation, bringing about local immuno-suppression possibly by the HLA linked mechanism.

As in the female, there is an increasing tendency for puberty to occur earlier in males, and so it is worth enquiring about a history of mumps or other viral infections after the age of ten.

Other viruses, including those causing glandular fever (infectious mononucleosis) may also be associated with clinical or sub-clinical orchitis and damage. This has also been reported with herpes, coxsackie, arbo, Dengue and Marburg viruses. The testes can later in adult life be affected by nephritis, prostatitis, vesiculitis, and epididymitis, especially with gonorrhea, chlamydia and other causes of non-specific urethritis, all of which should be excluded in the routine history.

It should be recognized however that quite often these infections may be asymptomatic, or obscured by other prostatic or urinary symptoms, so that the relevant history may not be reported. The clinician should however have a high index of suspicion in patients who have been sexually very active with multiple partners, especially where there is unexplained testicular atrophy or epididymal cysts.

Non-specific granulomatous orchitis is uncommon, and thought to be caused by an autoimmune response. During the acute phase of orchitis the testis is usually swollen, hard and tender, but in the chronic stage it may be atrophied and soft. It is of interest that during the acute stage, testosterone may be reduced, and FSH raised as a marker of damage to the germinal epithelium.

Non Alcoholic Fatty Liver Disease (NAFLD)

NAFLD is the most common liver disorder in Western industrialized nations. A recent study using the National Health and Nutrition Examination Survey (NHANES) found a 30% prevalence of NAFLD in the United States. It is related to insulin resistance and the metabolic syndrome and may respond to treatments originally developed for other insulin-resistant states including Type 2 diabetes, sudden weight loss, and treatment with metformin and thiazolidinediones.

One debated mechanism proposes a "second hit", or further injury, enough to cause change that leads from hepatic steatosis to hepatic inflammation. Hormonal imbalances, oxidative stress, and mitochondrial abnormalities have been put forward as potential causes for this "second hit" phenomenon.

Drugs

Many studies have recorded the increase insulin resistance caused by the extreme reduction in testosterone caused by androgen deprivation therapy (ADT) [26]. Many therapeutic agents can predispose to or precipitate diabetes, especially when pre-existing risk factors are present, and these may cause glucose control to deteriorate if administered to those with existing diabetes.

They may act by increasing insulin resistance, by affecting the secretion of insulin, or both. For convenience, these agents may be subdivided into widely used medications that are weakly diabetogenic, and drugs used for special indications that are more strongly diabetogenic. Examples of the former include antihypertensive agents and statins, and examples of the latter include corticosteroids, antipsychotics and a range of immunosuppressive agents. There are also a number of known beta cell poisons including the insecticides Vacor, alloxan and streptozotocin.

Taking statins can lead to weight gain, raised blood sugar levels, and also increase the chances of getting type 2 diabetes, according to some studies. It is considered that taking some statins impairs the function of the beta cells in the pancreas. There is also evidence that statins like Atorvastatin, can decrease the body's sensitivity to insulin.

Pesticides

A study by the National Institutes of Health (NIH) found that workers with regular exposure to pesticides to be at a greater risk of type-2 diabetes. Those who had used the insecticides aldrin, chlordane, and heptachlor more than 100 lifetime days had 51%, 63%, and 94% increased odds of diabetes, respectively [27].

Similarly, using cross-sectional data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES), reported a strong correlation between insulin resistance and serum concentrations of persistent organic pollutants (POPs), especially for organochlorine pesticide compounds [28].

Many agricultural pesticides, including some previously untested and commonly found in food, disrupt androgen levels, and it has been recommended that all pesticides in use today be screened to check if they block testosterone and other androgens Thirty out of 37 widely used pesticides tested blocked or mimicked male hormones. Sixteen of the 30 had no known hormonal activity until now, while there was some previous evidence for the other 14. Most of the newly discovered hormone disruptors were fungicides applied to fruit and vegetable crops, including strawberries and lettuce. 'Our results indicate that systematic testing for anti-androgenic activity of currently used pesticides is urgently required' [30]. This is especially as associations between androgen deficiency, Alzheimer's disease and Parkinson's have also been reported [31].

The position is well summarised, and a mechanism suggested, in a recent article in Toxicology Letters [32], which states 'For the main neurodegenerative diseases such as, Parkinson's disease, Alzheimer's disease and Amyotrophic Lateral Sclerosis there are evidences linking their etiology with long-term/low-dose exposure to pesticides such as paraquat, maneb, dieldrin, pyrethroids and organophosphates. Most of these pesticides share common features, namely the ability to induce oxidative stress, mitochondrial dysfunction, alpha-synuclein fibrillization and neuronal cell loss'. There is evidence that the anti-androgenic properties of many of these products may also play a part.

Pathology linking diabetes and androgen deficiency

As in diabetes, there can be genetic pre-dispositions to androgen deficiency, both racial and familial, which interacts with lifestyle and disease-related factors. Similarly, after a period of compensation, the ability of the testis to overcome the androgen resistance may fail, with structural changes in the Leydig cells, and signs and symptoms of endocrine failure developing.

In particular, there is a similarity between the changes observed in the testis with aging and with the pancreatic islets in maturity onset diabetes. Type 2 diabetes is associated with raised and then lowered insulin levels, combined with insulin resistance. This is due to the failure of beta-cell compensatory hypertrophy or hyperplasia. Prolonged stimulation of the beta-cells depletes the insulin granule stores and causes amyloid deposition in the islets (glucotoxicity). Beta-cells become unable to secrete pulses of insulin and are then “blind” to changes in glucose concentration. Hyperglycemia also contributes to insulin resistance as a result of down-regulation, with decreased numbers of glucose transporters (GLUTS) in peripheral tissues.

Similarly, Leydig cell hyperplasia is often found in patients with testicular atrophy, androgen insensitivity syndrome [33], and in chronic exposure to toxic chemical agents [34]. Contributory factors in relation to this pathology are reduced testosterone synthesis and impaired regulation of the hypothalamo-gonadal axis with aging, decreased sensitivity and numbers of AR, and inhibition of 5a-reductase and aromatase activity.

Such Leydig cell micronodules have been associated with significantly increased total Leydig cell volume, and showed evidence of functional Leydig cell failure, shown by vacuolization and a decreased T/Leydig cell volume ratio. The T/LH and T/FSH ratios were also significantly decreased, indicating an impaired testicular function at the endocrine as well as the spermatogenic level [33].

Lifestyle factors in metabolic syndrome and alcoholism cause fibrosis and damage to both pancreatic islets and Leydig cells, and can be modified with benefit to both conditions.

Just as there are different degrees of insulin resistance with effects on glucose and lipids, level of onset for different symptom thresholds may vary with androgen levels [35], and time for recovery of different functions causing a time dependant onset of effect. For example, libido is commonly restored in the first month, and energy levels rise within 2 months. Erectile function is commonly slower and may take 3 to 6 months, with obesity even slower at 6 months and bone density increasing at 9 months.

Measuring Testosterone Resistance

While tests for insulin resistance in relation to glucose metabolism, such as the hyperinsulinaemic glucose 'clamp' technique, have been well established for many years, recently there have been consistent observations of defective regulation of FFA and glycerol metabolism made possible by low dose insulin infusion techniques [36].

These are apparent even in patients in whom glucose tolerance was either normal or only marginally impaired as shown by investigations of insulin action in vivo using a low-dose incremental insulin infusion technique. This technique permits examination of circulating insulin/metabolite dose-response relationships within the lower physiological range of plasma insulin concentrations.

Using this approach, multiple abnormalities in the regulation of carbohydrate and lipid metabolism have been identified in subjects with a diverse array of insulin-resistant states characterized by variable degrees of glucose intolerance. These studies indicate that defective insulin action is not confined to impaired glucose disposal in insulin-resistant disorders and is usually evident in other aspects of intermediary metabolism. It is suggested that the

concept of insulin resistance as a pathological entity would be usefully enhanced by greater recognition of the multiple defects in insulin action which may be encountered in insulin-resistant states.

Similarly with testosterone resistance there are likely to be multiple defects in energy metabolism in different organs due to the diverse effects of testosterone on stem cells and those arising from them in virtually all tissues in the body (Figure 4) [37]. In the testosterone resistant state, there is an increase in the number and activity of adipocytes, particularly in abdominal fat, with enhancement of all the manifestations of the metabolic syndrome.

While it is possible to carry out measurement of some of the factors involved in testosterone resistance such as the binding protein SHBG which can be included in the calculation of 'Free Testosterone', oestrogen, and both CAG and GGN repeats, this still leaves a wide range of other factors which are unquantifiable (Figure 5) in routine clinical practice because of the multiple levels at which it occurs [2].

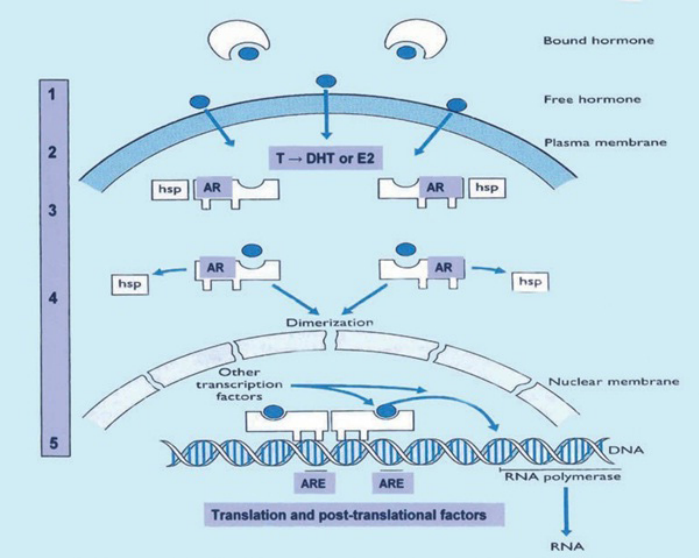


Figure 5: Levels at which androgen resistance can occur.

Androgen resistance affects virtually every system in the body and therefore results in diverse symptoms, causing a characteristic 'Testosterone Deficiency Syndrome' (TDS). The patient is aware of these symptoms, which can be quantified by standardised and fully validated questionnaires such as the Aging Male Symptoms Scale (AMS) questionnaire [38]. The AMS scale shows a convincing ability to measure treatment effects on quality of life across the full range of severity of complaints. Effect modification by other variables at baseline was not observed. In addition, results of the scale can predict the subjective clinical expert opinion on the treatment efficiency [39].

Some measure of testosterone resistance can be obtained by measuring the duration of action of a therapeutic trial of a standard dose of testosterone. It is commonly observed in treating patients with what could be called Type 1 testosterone deficiency eg due to non-descent of testes, that a small dose of pellet implants eg 4 four 200mg pellets is sufficient to cause full symptom remission for 6 months or more, and that TDS symptoms return only when the testosterone has fallen to low levels. As these patients age, the dose required rises, eg to eight or even ten 200 mg pellets, and the duration of action of even this increased amount lasts for a decreased period eg 4 months. Conversely, the testosterone level at which symptoms return rises gradually but characteristically in each patient [40]. 'Each person had a consistent testosterone threshold for androgen deficiency symptoms that differed markedly between individuals'.

More recently it has been observed that a standard intramuscular 1G dose of testosterone undecanoate (Nebido) lasts 3-4 months in young 'Type 1' testosterone deficient patients, but only 6-8 weeks in Type2 patients, particularly when the resistance is due to severe stress. Measuring the duration of action of an initial 'therapeutic trial' of injected testosterone undecanoate could be the best overall indicator of testosterone resistance.

Conclusions

Consideration of the many parallels between insulin and testosterone deficiency has wide-spread implications for the aetiology, diagnosis and treatment of the two overlapping conditions.

Both conditions can arise from genetic, ethnic and familial background influences. Environmental toxins such as pesticides can have an effect from intra-uterine life onwards. Infectious agents such as the mumps virus can damage the both the pancreas and testis. The effects of aging, especially combined with obesity, can gradually escalate this underlying hormonal deficiency by increasing resistance to their actions until overt pathology appears above the clinical horizon.

Diagnosis of testosterone deficiency can be delayed by over-reliance on laboratory rather than clinical data. Historically, without simple blood sugar and glucose tolerance tests, measurement of insulin levels alone, and the finding of normal or even elevated levels in maturity onset diabetes might have delayed its laboratory diagnosis by many years and given rise to confusion over its causation. Similarly over-reliance on total testosterone levels, and playing down the manifest and highly characteristic symptoms which can be quantified by fully validated questionnaires such the Aging Male Symptom (AMS) scale[38], as being 'non-specific' in relation to so-called normal ranges, results in failure to diagnose the relative lack of testosterone causing them, and prevents in the majority of patients being denied treatment.

Treatment of both diabetes and androgen deficiency is now more directed towards decreasing resistance to both hormones. In both conditions, life-style modification to cause weight loss and increasing physical activity, though difficult to achieve, can be highly effective. These measures contribute to increasing hormone levels and decreasing resistance to their action, as well as improving the patient's quality of life. Where you have multiple manifestations of the metabolic syndrome, syndrome X or what

might now be called 'syndrome Y' if you include the influence of testosterone regulated by the Y chromosome governing its production and action, it seems best to attempt to influence the underlying condition. Restoring insulin and testosterone activity simultaneously treats all the metabolic defects, and related clinical conditions, including diabetes, abdominal obesity, hyperlipidaemia, hypertension, androgen deficiency and the multiple diseases arising from them, without the need for polypharmacy [41,42].

Perhaps it is time to take a broader view of the multiple metabolic defects caused by resistance to both insulin and testosterone. Because of similar causation and co-existence of resistance to these two hormones in metabolic syndrome it is suggested that this may be new facet of the condition which because of its association with the male chromosome could be re-named as Syndrome-Y.

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