UK NATIONAL CONGRESS OF MEN’S HEALTH
LEEDS, BRISTOL & LONDON, UK

MEETING REPORT

MEETING INITIATED AND FUNDED BY BESINS HEALTHCARE

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Introduction from the Chairman

"We ignore men’s health at our peril,” said Dr David Edwards, chair of the congress, welcoming GPs, consultant urologists, diabetologists, nurse specialists and psychosexual therapists, to the UK National Congress of Men’s Health 2016. The meeting provided the opportunity to hear from leading experts about evidence-based approaches to optimising patient care and outcomes in this often overlooked field and to address the stark realities resulting in shorter life expectancy in men than women.

“There's more to testosterone than just sex,” suggested Dr Edwards. Underlining the reason why men’s health should be taken seriously by healthcare professionals he pointed out that sexual problems can be ‘harbingers of doom,' signalling wider health problems so health professionals need to be more proactive in screening men’s health. “It is a challenge, because men are reluctant to see the GP or practice nurse,” he noted.

Lack of awareness about low testosterone contributes to delayed diagnoses and inappropriate management. “Healthcare professionals need comprehensive consultations to help men to discuss this type of problem,” he told the meeting, noting that a man’s partner can be a valuable catalyst to encourage them to seek help. A recent UK survey of men diagnosed with hypogonadism revealed that low testosterone is under-recognised and that misperceptions and embarrassment can discourage men from seeking help.

Erectile dysfunction and loss of libido were key drivers for men to seek help, but Dr Edwards reported that patients also present with a wide range of other non-sexual symptoms. Even when hypogonadism was correctly diagnosed the survey findings showed that a substantial proportion of men received inappropriate or no medical treatment. “The survey findings highlight the need for improved awareness and management of low testosterone in men,” he concluded.

AGENDA

Introduction from the Chairman
Dr David Edwards, GP with a Special Interest in Sexual Dysfunction, Chipping Norton, Oxfordshire and Past-President of the British Society of Sexual Medicine

The state of men’s health: where are we now?
Professor Mike Kirby, Visiting Professor, Faculty of Health & Human Sciences, University of Hertfordshire & The Prostate Centre, London

Testosterone deficiency (TD) in primary care: recognising and managing
Dr Janine David, GP in Porthcawl, S Wales and Fellow of the European Committee of Sexual Medicine (FECSM)

How to diagnose and treat TD
Dr Jonny Coxon, GP in Brighton and Fellow of the European Committee of Sexual Medicine (FECSM)

Testosterone: laboratory perspectives, variation in practice and real world considerations
Dr Adrian Heald, Consultant in Diabetes and Endocrinology, Leighton and Macclesfield Hospital, Cheshire

Addressing the myths 1: testosterone and prostate cancer
Professor Abraham Morgentaler, Director, Men’s Health Boston & Associate Clinical Professor of Surgery (Urology), Beth Israel Deaconess Medical Centre, Harvard Medical School (Boston, USA)

Addressing the myths 2: testosterone and CVD
Professor Abraham Morgentaler, Director, Men’s Health Boston and Associate Clinical Professor of Surgery (Urology), Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, USA

Testosterone replacement in the older man
Professor Geoff Hackett, Consultant in Sexual Medicine, Good Hope Hospital, Birmingham and Professor of Men’s Health, University of Bedfordshire

Summary of 2015 consensus meeting resolutions on the management of TD
Professor Abraham Morgentaler, Director, Men’s Health Boston and Associate Clinical Professor of Surgery (Urology), Beth Israel Deaconess Medical Centre, Harvard Medical School (Boston, USA)
Professor Geoff Hackett, Consultant in Sexual Medicine, Good Hope Hospital, Birmingham & Professor of Men’s Health, University of Bedfordshire

References
THE STATE OF MEN’S HEALTH: WHERE ARE WE NOW?

“Being a man is a significant health risk, and men’s health is often ignored,” Professor Mike Kirby told the meeting. A recent report, The State of Men’s Health in Europe, warned of the ‘high level of preventable premature morbidity and mortality in men’, which it said would only be addressed by ‘targeted activity across the lifespan.’ The report found that poor lifestyle and preventable risk factors were some of the main causes of premature death and morbidity in men and estimated that more than 50% of deaths were avoidable. Gender differences in these risk factors contribute to the gap in life expectancy between men and women, which shows no sign of narrowing.

What is the solution? “We must make every consultation count,” Professor Kirby argued. When men do see their GP it tends to be for troublesome lower urinary tract symptoms (LUTS), anxiety about prostate cancer or bothersome sexual dysfunction. He suggested this provides the opportunity to evaluate cardiovascular risk, diagnose cancer early and talk about lifestyle. The close link between ED and CVD is well established, with a systematic review of more than 97,000 patients showing that those with ED had a 44% increased risk of cardiovascular events compared to those without ED. A study in men attending cardiac rehabilitation found that ED occurred five years, on average, before CVD. Researchers identified that opportunities to assess CVD risk and treat to goals had been missed in half of these men. “ED is a barometer of men’s health,” said Professor Kirby.

Obesity is an important risk factor for men’s health, with particularly high rates in the UK. Visceral fat is an active endocrine organ, modulating a wide range of molecular factors that result in inflammation, cancer, atherosclerosis, thrombosis, type 2 diabetes, low testosterone, atherogenic dyslipidaemia and hypertension. Professor Kirby suggested that checking testosterone can provide information on the self-perpetuating pathogenic cycle associated with central obesity (see Figure A). Metabolic syndrome – abdominal obesity plus any two of the following: elevated triglycerides, reduced HDL-cholesterol, raised blood pressure and raised fasting plasma glucose – is becoming increasingly prevalent among men and a study has shown that the relative risk of hypogonadism (total testosterone < 8.0 nmol/L) increased with the number of components of metabolic syndrome.

WHY CHECK TESTOSTERONE? A SELF-PERPETUATING PATHOGENIC CYCLE?

Once identified, health conditions and risks in men should be addressed with appropriate lifestyle interventions and prescription treatments. “Summing up, Professor Kirby concluded, “Men need to be encouraged and supported to take better care of their own health and health practitioners should take greater account of the specific needs of men and boys in service delivery, health promotion and clinical practice.”

Figure A
WHY CHECK TESTOSTERONE? A SELF-PERPETUATING PATHOGENIC CYCLE

**THE STATE OF MEN’S HEALTH: WHERE ARE WE NOW?**

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TESTOSTERONE DEFICIENCY (TD) IN PRIMARY CARE: RECOGNISING AND MANAGING

There is considerable uncertainty among health professionals on when to suspect testosterone deficiency (TD) how to test for testosterone, how to treat low testosterone and how to monitor treatment, warned Dr David. Underlining why testosterone levels are important, she noted that levels of the hormone have far wider health effects in men than sexual functioning. Research has shown that low serum testosterone is associated with:

- increased risk of developing metabolic syndrome\(^\text{10}\)
- obesity\(^\text{1,12}\)
- type 2 diabetes\(^\text{11,12}\)
- increased cardiovascular disease risk\(^\text{11,12}\)
- erectile dysfunction\(^\text{13}\)
- depression\(^\text{13}\)

In addition, low testosterone levels have been reported in up to 20% of men with symptomatic vertebral fractures and 50% of elderly men with hip fractures\(^\text{14}\).

**How is testosterone deficiency defined?**

TD is a clinical and biochemical syndrome characterised by a deficiency of testosterone, or testosterone action, and relevant symptoms and signs\(^\text{15}\).

She reported the prevalence of symptomatic TD in men over 40 is in the range of 2-6%, increasing with age, and is higher in some groups, with figures from NHS Diabetes indicating that 16% of men with type 2 diabetes have lower than normal testosterone levels and a further 24% have borderline low levels\(^\text{16}\).

TD also known as hypogonadism is currently underdiagnosed because men are embarrassed to talk about possible symptoms, the perception that symptoms are simply due to ageing and lack of awareness among health professionals. A recent UK survey of men with TD found that 55% waited between 3 - 24 months before seeking advice for symptoms and 35% waited for more than two years\(^\text{1}\). Even when TD is clinically diagnosed, many men are not treated with testosterone replacement therapy (TRT), warned Dr David. The UK survey found that 38% of men diagnosed with TD did not receive TRT. Of these, 31% did not even discuss TRT with their doctor\(^\text{1}\).

The REVITALISE Audit in the UK\(^\text{17}\) evaluated the treatment of patients diagnosed with ED either with or without type 2 diabetes in 13 general practices and found that more than one in three (33.5%) of the 3185 men with type 2 diabetes included had not been asked about ED, even though this is recommended in guidelines\(^\text{18}\). In addition, nearly two-thirds (64%) of the 1097 men that were diagnosed with ED had not had a testosterone test. Further findings showed that 80% of the 125 patients with ED and confirmed low testosterone (<12nmol/l) were not prescribed testosterone\(^\text{17}\).

TD can be primary, where the abnormality is in the testes, such as Klinefelter’s syndrome, and secondary, where the problem lies above the level of the testes. A wide range of drugs affect testosterone levels, including opioids, glucocorticoids, antidepressants, finasteride/dutasteride, carbamazepine and some other anti-epileptics, previous anabolic steroid abuse, antiretrovirals and statins\(^\text{12,20,21}\).

HOW TO DIAGNOSE AND TREAT TD

TD is associated with a wide range of signs and symptoms (see Figure B), increasing in prevalence with decreasing testosterone levels. He suggested that the ADAM questionnaire can be helpful in identifying features of TD.

The diagnosis of hypogonadism is based on:

- Signs and symptoms
- Low testosterone levels measured on two or more separate occasions\(^\text{22,23}\).

TD – SIGNS AND SYMPTOMS

Testosterone levels follow a circadian rhythm so should be measured between 7 and 11am. Testosterone occurs in the blood as free testosterone (2%); albumin-bound testosterone (38%); and sex hormone binding globulin (SHBG)-bound testosterone (60%). Ageing is associated with a ‘double whammy’ of falling total testosterone and increasing SHBG, which together contribute to decreasing free testosterone levels.

Guidelines recommend that patients with total testosterone below 8nmol/l will usually benefit from testosterone substitution. A short therapeutic trial (up to 6 months) may be justified in patients with borderline serum testosterone levels (8-12 nmol/l) and a clinical picture of TDS, while it is not usually required in patients with levels above 12nmol/l\(^\text{24}\).

Laboratories vary in the cut-off level that they give for low total testosterone. It is often 8 or 10nmol/l but is only 6.7nmol/l in Wales. This means many symptomatic patients are being left untreated. Dr Coxon recommended that GPs consider repeating the testosterone test and testing for SHBG, as well as calculating free testosterone in patients with total testosterone between local laboratory cut-off values and 12nmol/l (online free testosterone calculator www.issam.ch/freetesto.htm). If free testosterone is below <0.225nmol/l then patients should be treated “Don’t just treat the lab value. Consider the symptoms and treat the patient accordingly,” he advised.

She reported the prevalence of symptomatic TD in men over 40 is in the range of 2-6%, increasing with age, and is higher in some groups, with figures from NHS Diabetes indicating that 16% of men with type 2 diabetes have lower than normal testosterone levels and a further 24% have borderline low levels\(^\text{16}\).
The goal of TRT is to restore testosterone levels to the mid-normal range and alleviate signs and symptoms of TD without significant side-effects or safety concerns. Patients should be monitored to achieve testosterone levels of approximately 15nmol/l. Prostate specific antigen (PSA) should be measured at 3, 6 and 12 months and then annually, in addition to monitoring full blood count (FBC). TRT should be stopped if there is no symptom improvement after 6 months.

Follow-up of patients on TRT should include measuring testosterone, haematocrit, PSA and lipids for:
- Gel TRT - in the morning after application
- Short-acting injection – midpoint of the cycle
- Long-acting injection – trough level

Patients who respond positively to TRT may continue treatment with a standardised monitoring plan, checking that testosterone levels are optimal and ensuring any potential adverse effects are detected early.

"GPs have lacked confidence in treating testosterone deficiency but I think many are becoming more confident," said Dr Coxon. Guidance recommends that the majority of men with TD can be effectively assessed and managed by generalists. The exceptions are men with fertility issues, a diagnosis of prostate cancer, polycythaemia and those with other endocrinopathies.

"At present, symptomatic TD is frequently undiagnosed and left untreated," Dr Coxon warned. He pointed out that untreated TD can compromise a man’s sexual function, body composition, cardiometabolic profile and healthy ageing. "Testosterone therapy alleviates many of the symptoms of TD in hypogonadal men, resulting in improved physical health, mental health, sexual function and quality of life," he concluded.

TREATING TD

Treatment includes:
- Non-pharmacological treatment – including addressing sleep apnoea, weight reduction and lifestyle modification, which can all improve testosterone synthesis
- Treatment of co-morbid conditions, including review of medication that is contributing to TDS
- Testosterone replacement therapy (TRT)

TRT is available in a range of preparations, with different routes of delivery, ease of use, pharmacokinetics and cost. "Achieving good compliance is crucial," Dr Coxon told the meeting.

**Oral testosterone preparations** Advantages are the convenience of taking an oral preparation and modifiable dosage. Disadvantages include having to take it two to four times a day with meals and variable serum testosterone levels and clinical response.

**Transdermal testosterone** is available as gels. Advantages are flexible dose modifications, not requiring needles, achieving a rapid steady state and ease of withdrawal. Disadvantages include variable absorption and the risk of possible transfer during intimate contact.

**Intramuscular testosterone** can be given every three-weeks. This option is low in cost but considerable fluctuations in testosterone levels occur between injections. Long-acting intramuscular testosterone is given every 10-14 weeks, requiring fewer injections and maintaining a better steady state of testosterone levels. However, the injection site may be painful and the treatment cannot be withdrawn quickly.
"For a number of years I have been of the view that we should be screening men for low testosterone," suggested Dr Heald, adding, "We know that low testosterone, particularly in men with type 2 diabetes, is a risk factor for a range of conditions including cardiovascular events."

Focusing on laboratory measurement of testosterone levels, he explained that assays for testosterone in plasma and evaluation of results pose several challenges. Total testosterone concentrations in plasma vary by over three orders of magnitude depending on age, gender and the presence of diseases. The circadian rhythm for total testosterone means that levels vary with the time of day, with the best time of day to test being 7-11am.

A key challenge in interpreting testosterone levels is the general lack of age- and gender-corrected normal ranges using a standardised assay. Reference values are needed for laboratory tests and a patient's results are not medically useful if there are no data for comparison. "But we ideally want to know what is normal for an individual patient," explained Dr Heald.

Laboratories typically measure total testosterone and derived free testosterone. A venous sample for total testosterone should be taken before 11am. Levels should be assessed on at least two separate days, taking note that levels can fall with systemic illness and increase after sexual intercourse the night before. "There are no clear cut-offs of total testosterone below which a man can be confidently diagnosed as having hypogonadism," Dr Heald cautioned. "If a patient is at the lower end of the reference range and is symptomatic then we need to think seriously about whether they may be hypogonadal," he suggested.

International and European guidelines consider there are no generally accepted lower limits of normal ranges using a standardised assay. Reference values are needed for laboratory tests and a patient's results are not medically useful if there are no data for comparison. "But we ideally want to know what is normal for an individual patient," explained Dr Heald.

Professor Morgentaler reported that in 1992 he began performing prostate biopsies in apparently ‘normal’ men with low testosterone before giving testosterone therapy in order to rule out prostate cancer. All of the men had low testosterone, PSA values less than 4.0 and normal findings on digital rectal examination. Prostate biopsies revealed 11 cancers in the first 77 men tested, giving a rate of 14%. "This was the first data to put a chink in the story that high testosterone causes prostate cancer" he said. "Our results looked like low testosterone might be a risk factor for prostate cancer." In a review of the potential risks of testosterone replacement therapy published in 2004 he found no studies demonstrating that TRT causes progression of prostate cancer.

Exploring the literature that had led to concerns about testosterone therapy in men with prostate cancer, Professor Morgentaler noted that a study published in 1941 suggesting “cancer of the prostate is activated by testosterone injections” was based on a single patient treated with testosterone for 14 days. Considering the thinking that may have underpinned this hypothesis, he suggested that it seemed to make sense based on the fact that reducing testosterone was effective in treating metastatic prostate cancer. However, current studies show no significant relationship between androgens and prostate cancer risk.

A global pooled longitudinal study comparing 3886 men with prostate cancer with 6448 age-matched controls showed no association between testosterone levels and prostate cancer. There was no difference in the relative risk of prostate cancer between men with the highest 20% of testosterone levels compared to the lowest 20%. Results from prostate biopsies at two and four years in 3255 men in the placebo arm of the REDUCE trial, which investigated dutasteride for preventing prostate cancer, found that prostate cancer risk was not associated with serum testosterone or dihydrotestosterone (DHT). Men with high testosterone had no greater prostate risk than those with low levels. A meta-analysis of 19 placebo-controlled testosterone therapy studies in men with low or normal testosterone revealed no difference in prostate cancer, PSA levels over 4.0ng/ml or urinary symptom scores in those treated with testosterone compared to the placebo arm.

"But the dilemma is that LHRH agonists reduce PSA levels in prostate cancer, so clearly testosterone makes a difference," commented Professor Morgentaler. A study treating healthy young men with long-acting GnRH agonists showed no increase in PSA despite high levels of serum testosterone. This is explained by the fact that there are a finite number of androgen receptors so a saturation effect occurs at high levels of testosterone. Below the saturation point reducing serum testosterone reduces prostate cancer growth, but above this point increasing testosterone has no effect.
A study of PSA and testosterone levels in 2967 men, all with PSA < 4.0, being treated for sexual dysfunction revealed a saturation point at approximately 8nmol/L for testosterone. Above this level of testosterone the men showed no further increase in PSA (see Figure C). Findings from a study of 345 men with normal PSA values showed a higher rate of prostate cancer in those with lower total testosterone (<8.7 nmol/l) compared to those with testosterone (>8.7 nmol/l) (21% vs 12%, p=0.04)\(^4\). A similarly increased prostate cancer risk was seen in men with low free testosterone compared to those with higher levels. Multiple studies have shown an association between low testosterone levels and several features of prostate cancer, including higher grade, advanced stage at surgery, increased risk of recurrence after surgery and decreased survival.

**Figure C**

**PSA and Saturation**\(^3\)

**Summing up,** Professor Morgentaler said, “There is no evidence that high testosterone causes prostate cancer and low testosterone is not protective.” He suggested that the evidence is consistent with a saturation curve for PSA response to testosterone and potentially also for prostate cancer growth. He noted that low free testosterone is associated with more aggressive prostate cancer, “I’m not worried about high testosterone anymore, I’m worried about low testosterone.”

**Please note:** Testosterone replacement therapy is contraindicated in cases of known or suspected prostatic cancer or breast carcinoma.

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**ADDRESSING THE MYTHS 2: TESTOSTERONE AND CVD**

Two recent studies hit media headlines after suggesting a potential association between testosterone levels and cardiovascular disease and led to the FDA launching an investigation into the risk of cardiovascular events with testosterone products\(^25,26,27\). However, Professor Morgentaler explained that these studies were flawed and conflicted with more than 100 studies showing no risk or cardiovascular benefits with testosterone therapy or higher endogenous testosterone. “The two studies contradicted a large body of evidence over the last 20 years showing that endogenous testosterone and testosterone therapy are protective,” he noted. Low testosterone levels are associated with increased: mortality, incidence of coronary artery disease, severity of coronary artery disease and atherosclerosis. Testosterone therapy improves risk factors, including fat mass, waist circumference and body weight and metabolic syndrome.

A retrospective study of 1031 testosterone-deficient men (<8.7 nmol/l) found mortality was halved in those treated with testosterone compared to those who were not (10.3% vs 20.7%, p<0.0001)\(^4\). A similar halving of mortality with testosterone therapy was seen in a UK study of 581 men with type 2 diabetes treated for low testosterone (6.4% vs 19.2%)\(^4\). Critiquing the two recent studies, Professor Morgentaler noted that the study by Vigen et al in 8709 men with low testosterone undergoing coronary angiography found a 29% increased cardiovascular risk rate at three years in men treated with testosterone compared to those who were not (25.7% vs 19.9%)\(^4\). They all had testosterone levels less than 10.4nmol/l before angiography. Checking the figures reported in the paper, he found there were 123 events in the 1223 men treated with testosterone and 1587 events in the 7486 men not receiving testosterone. “This gave an absolute rate of events of 10.1% in the testosterone-treated group and 21.2% in the no-testosterone group,” he pointed out, giving a halving of the event rate with testosterone in line with previous studies.

JAMA has now been petitioned to retract the study by 29 medical societies and more than 160 leading experts in the field.

The second study, by Finkle et al based on an analysis of insurance claims for 55 593 men showed a 36% increased rate of MI in the 90 days after men were prescribed testosterone compared to the 12 months before\(^4\). “However, the pre- and post-testosterone prescription periods are unrelated and comparing pharmacoepidemiology patterns to MI rates is meaningless,” stated Professor Morgentaler. “The period before prescribing testosterone reflects the willingness of doctors to offer new testosterone prescriptions to men with recent MI. It is not the naturally occurring MI rate because doctors do not give testosterone to men with recent MI.”

When the FDA reviewed four studies with a possible signal regarding CV risk, including the studies by Vigen and Finkle, it found several limitations and declined to add a warning to testosterone products on cardiovascular risk\(^4\). In terms of previous evidence, a meta-analysis of 11 previous studies showed that lower testosterone levels are associated with higher all-cause mortality\(^4\). The first large-scale study on venous thromboembolism (VTE) and testosterone in more than 30000 men diagnosed with and treated for VTE found no difference in VTE rate in men on testosterone therapy compared to those who were not\(^4\).

In addition, a recent retrospective analysis of 83010 men with low testosterone showed reduced mortality in men whose testosterone was normalised with treatment compared to those not treated (HR 0.44) and lower rates of MI (HR 0.76) and stroke (HR 0.64)\(^4\).

“In summary, there is no convincing evidence of increased cardiovascular risks with testosterone therapy. On the contrary, there appears to be a strong beneficial relationship between normal testosterone and cardiovascular health that has not yet been widely appreciated.”

**Please note:** In patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease, treatment with testosterone may cause severe complications characterised by oedema with or without congestive cardiac failure. In such case, treatment must be stopped immediately. In addition, diuretic therapy may be required TRT should be used with caution in patients with heart disease. (Testogel Summary of product Characteristics)
Very positive improvement in muscle strength and physical function. Diabetes in a UK general practice study. "Results showed low baseline testosterone was associated with reduced all-cause mortality, especially in men over 60," concluded Professor Hackett. Prospective data from the European Male Aging study for 2599 men aged 40-79 years found that men with severe late-onset hypogonadism had a five-fold higher risk of all-cause mortality (hazard ratio 5.5). Men with testosterone levels less than 8nmol/L had twice the mortality risk compared to those who were eugonadal. Similar risks were seen for cardiovascular mortality. A large meta-analysis of 20 studies carried out between 1982 and 2005 showed consistently lower testosterone levels in men with type 2 diabetes and a recent general practice study screening men with type 2 diabetes showed around 40% had low total testosterone.

Reviewing the evidence for treating hypogonadism in older men, the largest study of testosterone treatment to be conducted in men aged 65 or older was recently published and showed significantly increased sexual activity (p<0.001), sexual desire and erectile function in those receiving testosterone gel for one year. There was no significant difference in the percentage of men with an increase of at least 50m in six-minute walking distance in the trial designed to assess this but combining the data for all 790 men in the study found that this was nearly twice as high in men receiving testosterone compared to those given placebo (20.5% vs 12.6%, p=0.005). Testosterone had no significant benefit on vitality but men treated with testosterone reported slightly better mood and reduced depressive symptoms.

A study of long-acting testosterone in men with type 2 diabetes and hypogonadism demonstrated significant reduction in the proportion with HbA1c > 7.5% at 30 weeks (p<0.007) and 82 weeks (p=0.009), in addition to weight, waist circumference and BMI. 46% of men reported a global improvement in health when asked, Professor Hackett reported. He noted that a meta-analysis has shown that intramuscular testosterone improves bone mineral density, particularly in the lumbar spine and the TOT trial showed a very positive improvement in muscle strength and physical function.

Testosterone replacement therapy was independently associated with reduced mortality in men with type 2 diabetes in a UK general practice study. Results showed low baseline testosterone was associated with increased all-cause mortality in men with type 2 diabetes and that TRT was independently associated with reduced all-cause mortality, especially in men over 60, concluded Professor Hackett.

"There is a myth that the benefits of testosterone are established in young men but not in older men," said Professor Hackett, but he reported a large body of evidence showing the association between late-onset hypogonadism with increased risks of all-cause and cardiovascular and benefits with testosterone treatment in older men.

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SUMMARY OF 2015 CONSENSUS MEETING RESOLUTIONS ON THE MANAGEMENT OF TD

An international group of experts in testosterone deficiency, encompassing a broad range of specialties including urology, endocrinology, diabetology, internal medicine and basic science research, from 11 countries met in October 2015 to address the concerns regarding testosterone. "Our goal was to see what we could all agree on, based on the evidence," explained Professor Morgentaler, who chaired the consensus meeting. Regarding terminology, the group agreed that testosterone deficiency (TD) is the preferred term for signs and symptoms related to low levels of serum testosterone and testosterone therapy (T therapy) is the preferred term for treatment with testosterone products.

The conference debated nine resolutions, and unanimously agreed:

- Testosterone deficiency is a well-established, clinically significant medical condition that negatively affects male sexuality, reproduction, general health, and quality of life. The consensus group found that research evidence shows that TD may predict increased risk of developing diabetes and metabolic syndrome. It contributes to decreased bone mineral density and is associated with increased all-cause and cardiovascular mortality.

- Symptoms and signs of TD occur as a result of low levels of T and may benefit from treatment regardless of whether there is an identified underlying etiology. Symptoms and signs of TD occur in healthy volunteers or patients who undergo androgen deprivation therapy and resolve with normalisation of testosterone. TD frequently occurs with conditions other than ‘classical’ causes, such as pituitary tumour, and there is no evidence to support restricting T therapy only to men with known underlying etiology. Newly recognised causes of TD include: diabetes, obesity, HIV/AIDS, glucocorticoids, opioids and ageing.

- Testosterone deficiency is a global public health concern. The prevalence in adult men ranges from 2% to 38% in studies from Asia, Europe, North America and South America.

- Testosterone therapy for men with TD is effective, rational, and evidence based. The expert group found high-level evidence showing that testosterone therapy effectively increases sexual desire (libido) and erectile and orgasmic function, increases lean body mass, decreases fat mass and improves bone mineral density.

- There is no T concentration threshold that reliably distinguishes those who will respond to treatment from those who will not. No study has revealed a single testosterone threshold that reliably separates men who experience signs and symptoms of TD from those who do not, nor those likely respond to treatment.
• There is no scientific basis for any age specific recommendations against the use of T therapy in men. The group found the concept ‘age-related hypogonadism’ to be of questionable validity because the decline in mean serum testosterone with age is minor and can be attributed to comorbidities, especially obesity. The evidence showed that older men respond well to T therapy, as do younger men. “It is illogical to single out TD as the one medical condition among many, including diabetes, hypertension, heart disease and cancer, that does not merit treatment because it becomes more prevalent with age,” pointed out Professor Hackett.

• The evidence does not support increased risks of cardiovascular events with T therapy. The media has focused on two observational studies that reported increased cardiovascular risks with T therapy but both of these had major flaws and limitations. Low serum T is associated with increased atherosclerosis, coronary artery disease, obesity, diabetes and mortality and several randomised trials in men with known heart disease have shown greater benefits with T compared to placebo. **Please note:** Testosterone replacement therapy is contraindicated in cases of known or suspected prostatic cancer or breast carcinoma.

• The evidence does not support increased risk of prostate cancer with T therapy. Serum androgen concentrations are not associated with increased risk of prostate cancer nor aggressive disease. T therapy shows no greater risk of prostate cancer than placebo. Research shows that aggressive/high-grade prostate cancer is associated with low serum T levels. **Please note:** Testosterone replacement therapy is contraindicated in cases of known or suspected prostatic cancer or breast carcinoma.

• The evidence supports a major research initiative to explore possible benefits of T therapy for cardiometabolic disease, including diabetes. A large body of evidence suggests that lower serum T concentrations are associated with increased cardiovascular risk and higher levels are protective. T therapy reliably increases lean mass, decreases fat mass and may improve glycaemic control. Observational studies show that mortality rates are reduced by half in men with TD who receive T therapy compared to those who are untreated.

**COMMON CONCERNS REGARDING TESTOSTERONE AND TESTOSTERONE THERAPY AND CONSENSUS CONFERENCE EXPERT RESPONSES**

<table>
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<tr>
<th>Concerns regarding TD and T therapy that have appeared in the scientific and lay media</th>
<th>Expert responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>The condition of low T does not exist</td>
<td>False. Low T is an informal term used to describe TD, much as “heart attack” is used in place of myocardial infarction. TD is a well-established medical condition described in all general medical textbooks</td>
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<tr>
<td>The symptoms of TD do not merit treatment, particularly decreased libido and fatigue</td>
<td>The symptoms of TD are of considerable importance to many affected men. However, decisions regarding treatment must be individualised</td>
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<tr>
<td>T therapy is risky</td>
<td>All medical treatments entail some degree of risk. Known risks of T therapy include acne, gynaecomastia, peripheral oedema, infertility, decreased testicular volume, and erythrocytosis. These are reversible with discontinuation of treatment. The evidence fails to support assertions that T therapy is associated with increased CV risk or prostate cancer</td>
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<tr>
<td>T therapy increases risks of VTE, such as deep venous thrombosis or pulmonary emboli</td>
<td>Available evidence reveals no increased risk of VTE with T therapy</td>
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<tr>
<td>T therapy increases the risk of myocardial infarction, stroke, and death</td>
<td>Two flawed studies reporting increased CV risk with T therapy received enormous media attention. One misreported primary results and the other had no control/comparison group. In contrast, several dozen studies provide high-level evidence that reduced T concentrations are associated with increased CV events and atherosclerosis, whereas T therapy appears to reduce CV risk or improve known CV risk factors</td>
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<tr>
<td>T therapy causes PCa to develop or become aggressive</td>
<td>Not supported by evidence. Longitudinal data reveal no relationship between higher serum T level and PCa risk. Meta-analyses found no greater risk of PCa in men who received T therapy compared with placebo. High-grade disease and poor prognostic PCa features are associated with low serum T concentrations</td>
</tr>
<tr>
<td>T therapy is experimental/investigational</td>
<td>False. T therapy has been a standard form of medical treatment for men with TD for more than 70 years, with numerous studies documenting benefits and a reasonable safety profile</td>
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<tr>
<td>The decline in T is due to normal aging and does not merit treatment</td>
<td>Age alone has little impact on serum T concentrations. Most of the age-associated decline in serum T levels is associated with development of comorbidities, especially obesity. Many important medical conditions are age related, including coronary artery disease, diabetes, arthritis, cataracts, and most adult cancers. We find no justification to single out TD as a condition that does not merit treatment because it becomes more prevalent with age</td>
</tr>
</tbody>
</table>
REFERENCES

2. EC. The State of Men’s Health in Europe 2011; 8, 17
8. The IDF Consensus worldwide definition of the metabolic syndrome; International Diabetes Federation 2006; 10
10. Antonio L et al. Journal of Clinical Endocrinology Metabolism 2015; 100: 1396-404
39. Finke WD et al. PLOS One 2014 doi.org/10.1371/journal.pone.0085805
40. FDA 2014
42. Neuroendocrinology 2013; 169: 725-733
47. Sing EL et al. Journal of American Medical Association 2006; 295: 1288-1299
51. Travers NJ et al Journal of Clinical Endocrinology Metabolism 2006; 91: 2026-2036

Abbreviated Prescribing Information Testogel® 50mg, gel in sachet

For full prescribing information, including side effects, precautions and contraindications, please consult the Summary of Product Characteristics (SPC).

Presentation: 5 g sachets containing 50 mg of testosterone. Indication: Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests. Dosage and administration: Cutaneous use. The recommended dose is 5 g of gel (i.e. 50 mg of testosterone) applied once daily. The daily dose should not exceed 10 g of gel per day. Adjustment of dosage should be in steps of 2.5 g of gel, usually based on measurements of serum testosterone concentrations. The gel should be administered by the patient himself, onto clean, dry, healthy skin over both shoulders or both arms or abdomen. Allow drying for at least 3–5 minutes before dressing. Contraindications: Cases of known or suspected cancer of the prostate or breast, known hypersensitivity to testosterone or to any other constituent of the gel. Warnings and precautions for use: Testosterone insufficiency should be clearly demonstrated by clinical features and confirmed by 2 separate blood testosterone measurements. Testosterone level should be monitored at baseline and at regular intervals during treatment. In addition patients receiving long-term androgen treatment the following laboratory parameters should be checked regularly: haemoglobin, haematocrit (to detect polycythaemia), liver function tests, lipid profile. Testogel may affect results of laboratory tests of thyroid function. Risk of pre-existing prostatic cancer should be excluded and the prostate gland and breast monitored during Testogel treatment. Testogel should be used with caution in cancer patients at risk of hypercalcaemia and associated hypercalciuria due to bone metastases; regular monitoring of serum calcium concentrations in these patients. Testogel may cause oedema with or without congestive cardiac failure in patients suffering from severe cardiac, hepatic or renal insufficiency or ischaemic heart disease. If this occurs, treatment must be stopped immediately. Testogel should be used with caution in patients with ischaemic heart disease. Testosterone may cause a rise in blood pressure and should be used with caution in men with hypertension. Irritability, nervousness, weight gain, prolonged or frequent erections may indicate excessive androgen exposure requiring dosage adjustment. Testogel should be used with caution in patients with epilepsy and migraine. Do not apply to the genital areas as the high alcohol content may cause local inflammation and associated close skin to skin contact. There is limited experience regarding safety and efficacy of Testogel in patients over 65 years of age. Testogel is not indicated for use in women or in children under 18 years of age. Testogel is not a treatment for male impotence or sterility. For further details refer to the SPC. Interactions: May increase the activity of oral anticoagulants. Concomitant administration of testosterone and ACTH or corticosteroids may increase the risk of developing oedema. Pregnancy and lactation: Pregnant women must avoid any contact with Testogel application sites. This product may have adverse uterine effects on the foetus. Undesirable effects: Local skin reactions include: erythema, acne, urticaria and dry skin. Systemic adverse reactions include: prostatic disorders, gynaecomastia, mastodynia, headache, dizziness, hyperaesthesia, paraesthesia, anemia, mood disorders, hypertension, diarrhoea, alopecia, polycythaemia, increased serum lipids increased haematocrit, increased red blood cell count and increased haemoglobin. Other known adverse drug reactions of testosterone: prostatic changes and progression of sub-clinical prostatic cancer, urinary obstruction, jaundice, changes in liver function tests, increased libido, nervousness, depression, sleep apnoea, muscle cramps, priapism and, during high dose prolonged treatment, electrolyte changes, olistospermia and priapism. In case of severe application site reactions, treatment should be reviewed and discontinued if necessary.


Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Besins Healthcare (UK) Ltd, 28 Polland Street, London, W1F 8QN. Tel: 0203 862 0920. Email: drugsafety@besins-healthcare.com