Mission: Healthy Men

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Misyon: Sağlıklı Erkek

Özet

Erkek sağlığı net tanımlamalar olmasa da tıp dünyasının yeni ilgi alanlarından biridir. Kadınlar özürlülük ve morbidite açısından daha fazla risk taşısa da erkekler kadınlardan daha erken ölmekte ve daha yüksek mortalite riski taşımaktadırlar. Yaşam süresinin uzunluğu açısından cinsiyet farklılıkları, çevresel, davranışsal ve biyolojik faktörlerin kompleks ilişkisiyle açıklanmaktadır. Erkekler, sağlık hizmetlerini çoğunlukla çocukluk veya yaşlılık döneminde kullanmakta, erişkin dönemde ise çok geç kalmakta ve bu durum erken ölümle de sonuçlanabilmektedir. Bu "erkekliğin bedeli" olarak adlandırılmaktadır. Erkeklerde erken mortalitenin belli başlı nedenleri kardiyovasküler hastalıklar, kanserler, inme, kazalar, yaralanmalar ve mental sağlık sorunlarıdır.

Erkekte sağlık farkındalığındaki bu boşluk cinsiyetle ilişkilendirilmiş ve "cinsiyet boşluğu" olarak adlandırılmıştır. Andropoz, yaşlanan erkekte androjen düzeylerinin düşmesiyle ilişkilidir. Andropozun klinik tablosundan sorumlu hormonlar, başta testosteron olmak üzere dehidroepiandrosteron, östradiol, kortizol, prolaktin, tiroksin ve büyüme hormonudur. Testosteron düzeyleri 50 yaşından sonra yılda yaklaşık %1 civarında düşmeye başlar. Andropoz semptomları, uyku bozuklukları, cilt ve tüylenmede değişiklikler, visseral yağlanmada artış, cinsel istek, erektil fonksiyon, entelektüel kapasite, kemik mineral yoğunluğu ve yağsız beden kitlesinde azalma olarak ortaya çıkmaktadır.

Eksilen androjenin yerine konmasında temel amaç testosteron düzeylerini mümkün olduğunca fizyolojik düzeye yaklaştırmaktır. Androjen reseptör ligandlarından biri olan selektif androjen reseptör modülatörlerinin kullanılmaya başlaması androjen tedavisinin geleceğini önemli ölçüde etkileyecek bir gelişmedir.

Yaşlanmanın getirdiği genel kronik değişiklikler ile cinsiyet hormonları ve diğer hormon sistemleri arasındaki kompleks ilişkiler nedeniyle normlar üzerinde uzlaşma zor olabilir. Erkekte hormonal değişikliğin zamana yayılması nedeniyle kolay tanımlanabilir olmaması, yaşa göre normal olan erkek endokrin karakterizasyonunun belirlenmesini zorlaştırabilir. Aile hekimleri, erkekleri, kendi sağlıklarının yönetimine katılmaları konusunda teşvik etmelidirler. Erkek sağlığındaki gelişmeler sadece erkek değil kadın sağlığının gelişimine de katkıda bulunacaktır.

Anahtar Kelimler: erkek sağlığı, androjen yerine koyma tedavisi, andropoz

Summary

Men's health is a new area of interest and it has no clear definition yet. Although women experience greater burden of morbidity and disability, men die younger than women and have a higher mortality. The gender difference in longevity is due to complex interaction of environmental, behavioral and biological factors. Men use health care services only when they are children/elderly and when they use it may be too late causing premature death. This is called "the cost of masculinity". The main causes of premature mortality in men are cardiovascular diseases, cancers, stroke, -accidental and non accidental- injuries, and mental health problems. The general lack of health awareness in men has been termed "the gender gap". Andropause is associated with androgen decline in the aging male. The recognized hormones whose changes are thought to drive the clinical picture in andropause are primarily testosterone and dehydroepiandrosterone, estradiol, cortisol, prolactin, thyroxine and growth hormone. Testosterone levels decrease after the age of 50 years at a rate of approximately 1% per year. Symptoms of andropause includes alterations in sleep patterns, body hair and skin, besides increased visceral fat and decreased sexual desire, erectile quality, intellectual capacity, bone mineral density and lean body mass. The major goal of androgen substitution is to replace testosterone at levels as close to physiological levels as is possible. Selective androgen receptor modulators are a novel class of androgen receptor ligands that might change the future of androgen therapy dramatically. Agreement upon norms is impeded by the complex interrelations of the sex hormones with other hormone systems, with common chronic conditions of aging. The fact that men lack a major, identifiable displacement in hormonal status makes the characterization of age-normal male endocrine status particularly difficult. General practitioners/family physicians should empower men to manage their own health. Improvements in men's health will have a beneficial outcome not only to the male but also to the female.

Key words: men's health, androgen replacement therapy, andropause

Men's health is a relatively new area of interest under

the scope of andrology that deals with male reproductive health including male sexual function/dysfunction, fertility/infertility, male reproductive endocrinology and general well-being[1]. Because of dramatic changes in the development of the age pyramid, there will be a tremendous change of the ratio old to young men within the next 20 years[2]. Therefore, consultations on the part of older men will greatly increase, particularly in terms of health prevention and hormone dysfunction.

In 2006, 11% of global population (688 million persons) was aged 60 years or more, 13% of these were 80 and over. There were 82 men for 100 women (?60 years old), 100 men for 120 women (?65 years old), 55 men for 100 women (?80 years old), 100 men for 250 women (?85 years old). In 2050, 22% of global population (2 billion people) will be aged ?60 years of age, 20% of these will be ?80 years of age. For the first time in the United States (US) history, older population will be larger than children's (0-14 years of age). Life expectancy in the Western world is 73.7 years for men and 83.8 years for women [76 vs. 80 years in the United Kingdom (UK)]. From 2001 to 2002 age adjusted death rates decreased by 1.3% for males and by 0.7% for females. For white males and females the age adjusted death rates decreased 1.1% and 0.5%, respectively. In 2006 the average life-expectancy for Russian men was 59 years while for women it was 13 years longer-72 years. The primary social determinants of the decline in male life-expectancy are unhealthy lifestyles, particularly excessive alcohol consumption accompanied by injuries and violence. Men's chronic illness and premature death have been called the "cost of masculinity"[3].

Wives' low education is positively associated with increased risk of mortality and cardiovascular disease (CVD) in their husbands[4]. Partner's education has also been shown to influence own self-reported health and to exert an indirect effect through household income and neighborhood characteristics[5]. Elevated spousal income increased men's odds of dying, while the inverse was true for women[6]. Lung cancer in women was very strongly associated with husband's occupation and ischemic heart disease and lung cancer mortality in women was mainly associated with husband's occupation[7]. Husband's lower education decreased women's risk of breast cancer mortality[7]. Wife's education was the strongest and only predictor of man's risk of death across all specific causes of death except stroke. Wife's low education was associated with increased risk of total mortality and CVD mortality of husbands[7]. Highly educated women have better health-this fact alone can reduce the burden on men married to highly educated women as well as increasing the quality of informal care provided by wives to men in case of illness. Wives might shape home life, life style and family health behaviors[7].

Men are more likely than women to be mentally ill and they are in greater risk of heart disease and stroke. Men in routine and manual jobs are more likely to smoke and have chronic health problems than other men. Diagnoses of both prostate and testicular cancer have increased since the early 1990s[8]. The suicide rate amongst young men has increased by 250% over the past two decades[8]. More than 60% of men are overweight or obese. Between the ages of 15 and 64 men attend their general practitioners (GPs) almost half as often as women[9]. The importance of gender and its influence on health had led to an increasing interest in gender-specific fields worldwide[10]. The percentage of men who have reported drinking as a problem was higher for married men. Younger men were more likely to wish to cut down the amount of alcohol they consumed and married men were more likely to remain at their present level[11]. Men have a higher incidence of stones in the urinary tract[12]. The gender difference in longevity is due to complex interaction of environmental, behavioral and biological factors. Women experience greater burden of morbidity and disability. Men die younger than women by about five years and have a higher mortality through all age groups. The reasons for premature mortality not fully understood.

Often gender is taken as being synonymous with "women's issues". Male health concerns have been neglected. The expectancy of life without disability is increasing slower than life expectancy. Average annual health care charges were much lower for persons at low-risk. The total charges for the men at low risk were less than two thirds of the charges for the men not at low risk ($1615 less) [13]. For the men at low risk, the mean serum cholesterol level was lower by 36 mg/dL (0.9 mmol/l). Systolic and diastolic blood pressures were lower by 28 and 13 mmHg respectively[13]. Men, regardless of risk status, spend more days in the hospital than women and have higher Medicare charges, for reasons not yet elucidated[13]. The mean difference in lifespan between women and men is 4.2 years. Projection for 2050 is 4.8 years. Oxidative damage to mitochondrial DNA is 4-fold higher in males. Lifestyle-related causes such as smoking, alcohol-related mortality (aggression, accidents, suicide) are more common in men than in women. Ischemic heart disease, hypertension, stroke, lung cancer are diseases whose primary prevention needs to be addressed. Prostate cancer, colorectal cancer, osteoporosis are conditions in which early diagnostic tests and screening procedures play an important role in secondary prevention and self-care strategies. The main causes of premature mortality and mortality in men are cardiovascular disease, cancers and accidental and non-accidental injury. Respiratory disease is also a major cause however it impacts more in the elderly[14]. The heart-watch program is showing gains to date of 522 life years gained (LYG) at a cost of less than 8000 euro per LYG[14]. The risk of cancer increases with age and almost doubles every 10 years. Up to age 60 the risk to women is higher, but after this becomes higher to men[14].

Health and safety in the work place has improved significantly, road accidents are a cause for concern especially among young men, suicides are an increasing cause for concern with a male to female ratio of over four to one. There are increasing and worrying trend towards addiction and substance abuse[14]. Improvements in men's health require a societal approach; this will have a beneficial outcome not only to the male of the species but also to the female. The active involvement of women in men's health is also to be welcomed. Men wish to be healthier, live longer and suffer less ill health[14].

Women visit the doctor 150% as often as men. Men cost the health services more than women since they seek medical services at a more advanced stage of disease. Natural aging process is genetically determined and cannot be changed today. Aging amplifiers (environmental and developmental

factors) can be modified. Acute or chronic illness or intercurrent diseases can be prevented, delayed or cured. Five out of six men in their 60s have one or more of these diseases. Educating both the public and health care providers about the importance of early detection of male health problems will result in reduced rates of morbidity and mortality as well as health costs for many age-related diseases. Surgically oriented urologists have arrived the same crossroad gynecologists reached 50 years ago.

Early identification and treatment of "diseases of the elderly" (such as hypertension, diabetes, and certain forms of cancer) are of essential importance. It may be useful to start nutriceutical intake rather early in life (between 40 and 50 years of age). Many men said that in actual practice male pleasure is most important[15]. Şöyle söylenebilir mi?: Although many men said that "in actual practice male pleasure is most important " it may be useful to start nutriceutical intake rather early in life (between 40 and 50 years of age).

Social pressure for sexual performance is placed on men[15]. Participants endorsed the norm that it is largely men who decide when sex will occur[15]. A study of healthcare needs in the general population had indicated that only a small proportion of patients seeking professional help for sexual problems actually received it[16].

Almost two third of GPs had cited lack of time or lack of competence as reasons for not actively interrogating a patient when an erection problem was suspected[17]. Substance abuse and male gender are considered to be risk factors for suicide[18]. Prevalence of substance abuse is approximately 5% for men[19]. Men in the US were found to be four times more likely than women to commit suicide[20]. Suicide attempts occurred at times when the men were experiencing major negative life events[18]. They feel physically and socially undesired[18]. Early experiences of emotional distress and the accumulation of negative life events seemed to create a form of existential chaos[18]. Health professionals should focus on individuals' struggle with interpersonal and intrapersonal stressors, identify metaphorical language, evaluate suicidal risk, create an interactive context, and recognize subjectivity.

What is the "gender gap" and how can GPs help close it? How can GPs help reduce mortality in young men?

There is an intrinsic difference in overall disease susceptibility between the sexes. Men do not care themselves as well as women do. This general lack of health awareness among males has been termed "the gender gap"[21]. Cardiovascular problems are the main cause of male deaths in the UK, closely followed by cancer. One in five men dies prematurely before the age of 75 from CVD. Men's greater susceptibility to heart disease has generally been ascribed to the lack of protective effects of estrogen[21]. Most of the preventable risk factors for myocardial infarction (MI) or stroke (related to smoking, central obesity and hypertension) are considerably more common in men than women. Of males, 10% have high blood pressure but not receiving treatment. A further 13% of men are currently being treated for high blood pressure but because of inadequate therapy half of these still have significant hypertension[21]. In primary care our task is to encourage people to have their risk factors addressed, to receive appropriate lifestyle advice and support, to continue to take appropriate medication to reduce their risks[21]. Prostate cancer is the second most common male cancer and a leading cause of cancer death. There are 15000 new cases per year and 10000 deaths per year in the UK[21].

Mortality in young men

The major causes in England and Wales are injury and poisoning including homicide, suicide and accidents. During 1992, deaths from injury and poisoning accounted for 52% of all deaths in the 15-39 years age-group in men[21]. Specific problems with young men are homelessness, drugs, and unemployment[21].

Eleven percent of men failed to receive at least 100% of recommended allowances (RDA) for protein[22]. There is a longitudinal decline in testosterone and an increase in LH and FSH in older men. The average rate of decrement in testosterone concentration was 110 ng/dL every decade[23]. Estimated iron stores were normally distributed (range: 50-1550 mg) with men having significantly higher mean estimated iron stores than women[22]. Men having either a single chromosomal 845A and/or 187G mutation results in higher "mean percent transferrin saturation" (PSAT's) and higher estimated iron stores if no HFE mutation was present[24]. Serum 25hyroxyvitamin D (25OHD) levels decline with aging[22].

Despite more than two decades of public health recommendations to vaccinate men making sex with men (MSM) against hepatitis B virus (HBV) fewer than 20% of MSM aged 23-29 years were immunized against HBV[25]. Sexual behavior and injection drug use continue to be associated with HBV transmission among MSM[26,27]. Human immunodeficiency virus (HIV) and sexually transmitted disease (STD) testing and treatment may be even more compromising for HBV infection prevention for men in their 20s than for younger men. Although the CDC guidelines for STD treatment have recommended routine Hepatitis A and B immunization for males making sex with men in addition to annual testing for HIV, syphilis, chlamydia and gonorrhea, CDC "HIV counseling and testing guidelines" do not include recommendations for HBV vaccination[28,29]. Participants reporting a regular source of health care had a higher prevalence of immunization[24]. Assessment of patients' risk behavior is recommended by the United States Preventive Services Task Force (USPSTF) and by professional medical organizations[30]. Less than 50% of patients were asked about sexual behaviors[31-34]. Addressing missed opportunities for HBV infection prevention in both primary health care and HIV and STD prevention systems could eliminate HBV transmission among MSM in the US[26].

In particular, the family physician should remain alert for signs and symptoms of substance abuse, domestic violence and depression[35]. Male patients with psychosocial dysfunction frequently mention vague complaints that do not easily fit into diagnostic categories[35]. The prevalence of drug, steroid and alcohol abuse has continued to increase at an alarming rate since the early 1990s. Recent studies indicate that 24% of the eighth graders and 38% of the tenth graders admit to using illegal substances in the previous year. A reported 5% of 12th graders use marijuana daily[36]. From 5% to 11% of adolescent males reported use of anabolic steroids[37]. Men are at greater risk for alcohol abuse, with the highest rates

of abuse occurring in men between 25 and 39 years of age[38]. Alcohol abuse is a problem in 14% of men more than 65 years of age and in 1.5% of women in the same age group[39].

In domestic violence episodes, the majority of assailants are men 18 to 35 years of age. Most of these men use alcohol or drugs on the day of the assault. Physicians should routinely screen male patients by asking if they ever feel the urge to strike out a family member when they are angry or frustrated[35].

"Male midlife crisis" or "male menopause"

The literature reveals very little scientific evidence for the existence of a "male midlife crisis" or "male menopause". However, in the transitional period between 40 and 60 years of age, men become aware that they are aging, that life is finite and that death will occur at some point in the not too distant future[35]. Men must deal with "empty nest syndrome", retirement, physical decline, unfinished tasks and plans, loss of parents, friends or even a spouse. Depression is an insidious and common finding in elderly men[35]. Approximately 1% of community-dwelling elderly men have major depressive illness, and from 13 to 27% has minor depression or subsyndromal depression[40-41]. The prevalence of major depressive disorders ranges from 5 to 50% in men and women who are institutionalized or have medical illnesses[40,41]. Depression is two to three times more common in women than in men but men are more likely to commit suicide. Unrecognized or undertreated depression unnecessarily increases suffering and health care utilization and decreases functioning and the quality of life (QoL)[35]. Risk factors for depression in men include previous depressive episodes, family history of depression, comorbid medical illness, medications (i.e. Beta blockers, histamine H2-receptor antagonists, methyldopa, benzodiazepines, reserpine and barbiturates), alcohol abuse, and lack of social support, recent life stressors, single marital status and physical disability. Advancing age itself is not a risk factor[35]. Suicide is a significant concern in depressed men. In particular, elderly white men have six times the suicide rate of the general population. From 1980 to 1992, the suicide rate increased 9% in persons 65 years and older and increased 35% in persons 80 to 85 years of age[41]. The likelihood of a suicide attempt resulting in death is highest in the elderly, increasing from 200 attempts for every one death in young adults to four attempts for every one death in the elderly[42].

Early genitourinary symptoms or problems in men may not be brought to the family physician's attention unless direct questions are asked to assess sexual and urinary function. Common genitourinary health issues in men include prostatitis, benign prostatic hyperplasia, urogenital cancer, premature ejaculation and erectile dysfunction. Screening questions directed at identifying these health problems should be included in the comprehensive health evaluation[43].

Obese men present with more advanced stage prostate cancer and have a higher risk of recurrence compared to non-obese men. Obesity is associated with a lower "risk" of early stage/less aggressive disease[44,45]. Serum prostate specific antigen (PSA) elevations greater than 4.0 ng/mL are associated with prostate cancer. The positive predictive value of a serum PSA value between 4-10 ng/mL is only 20-30%, >10 is 40-70%, <4 are not well defined[46].

Living alone was a significant predictor of mortality for middle-aged men but not for women. Men who live alone have about twice the risk to die from all causes and cardiovascular diseases, independent of cardiovascular disease risk factors, health behavior, co-morbidities and sociodemographic factors[47]. Men's reluctance to seek help and use health services is a concern across most western cultures[48]. Men are victims of their own behavior[49]. Men are ignorant about or disinterested in their health[50]. These conceptions have often been linked to hegemonic masculine traits that create an expectation on men to be independent, strong, stoical and tough[51]. Factors that influence men's help seeking practices are the length of available time to monitor health and to legitimate help seeking, previous illness experiences, maintainenance of regular activities, assessment of illness severity. In fact, no clear definition of "men's health" exists[52]. Males who adopt more traditional masculine roles are less receptive to health promotion messages and more involved in health-risk behaviors[53]. Men attend doctors less often and are less likely than women to report efforts to improve their health[54]. Hegemonic masculinity requires men to deny vulnerability, to be in emotional and physical control and to dismiss any need for help[55]. Positive body image has been established as an important issue in women's health and well-being, while comparable data about male body image is limited[56]. The men in higher skilled occupations had a better diet quality than those from lower skilled occupations. Those from "low occupational status" tend to be less worried about their nutrient intakes[57]. Physical activity levels were unsatisfactory. Rural men have poor dietary habits. A quarter of the men had more than four drinks on each drinking occasion[51]. Interestingly, almost 42% of men in the healthy weight range wanted to be heavier [58]. Providing health promotion activities in the workplace can increase accessibility to staff who may not use programs offered in conventional health or community settings or who may otherwise be time-poor[59]. Although the evidence for workplace health promotion programs is mixed, advantages to employers from having healthy, fit staff may include reduced absenteeism, lower accident rates and improved efficiency as well as increased staff interaction and morale[60].

Benign Prostate Hyperplasia (BPH) is the most common nonmalignant condition of the prostate occurring in aging men[61]. BPH is rarely seen in males less than 40 years of age. The incidence of BPH increases from 50% at 50 years and reaches 80% around 80 years[62]. BPH is a multifactorial disease including family history, race/ethnicity, immunological, endocrinal factors, dietary, metabolic (diabetes mellitus (DM), obesity, hypertension, ischemic heart disease, hyperinsulinemia, dyslipidemia) factors.

People with a high level of personal control are more likely to initiate preventive behaviors such as getting regular check-ups, adhere to health behaviors such as maintaining balanced diet and exercising and quit risky behaviors such as smoking, excessive drinking and substance abuse[63]. Popular culture appears to equate being male with a lack of regard for sleep[64]. The men do not care about sleep and sleep is an unwelcome "dead time" [65]. Dominant men are required to undertake socially masculinised, physically risky behaviors. Men see health as women's business and responsibility, know little about men's health, tend to keep

quiet about their health problems and to deny themselves as self-monitoring role (as doing health promotion is "female") [66]. To refuse taking sick leave from work, to insist that they need only few hours to sleep and to boast that drinking does not impair their driving are demonstrative for dominant norms of masculinity[55]. Tobacco and alcohol are often used as a means of coping with the self-perceived strains and pressures of work[67]. The men attempt to "balance both sides of dichotomy", between control and release or between moderation and excess, in order to maximize the possibilities for good health. Life course events, such as marriage and fatherhood, may play a key role in this balancing act[68]. Watson suggests that men have to "manage ambiguity" between how they define others' health and how they engage with their own health. He proposes the "male body schema" involving four different modes of embodiment: Normative (body stereotypes), pragmatic (idea of having a "normal" everyday body), experiential (primary site for experiencing emotions), visceral (relates to the "unseen", body you are born with) [69].

The South European countries report fewest cases of longstanding illness but have relatively large relative health inequalities. Italian men and women together with Spanish men, demonstrate smaller odds ratio than the other South European countries[70]. Polish men have higher odds ratio regarding the results of limiting longstanding illness. Hungarian women have higher odds ratio for self-assessed health. Odds ratios are among the smallest for Slovak men and women regarding self-assessed health[70]. South European welfare regimes have the largest health inequalities. Scandinavian welfare regimes are placed less favorably than the Anglo-Saxon and eastern European[70]. Men of many different cultures in the western world tend to delay visiting their doctor for longer and use their services less often than women[71]. Categorization by gender does not adequately explain why certain men visit their doctor more often, why some women are reluctant to seek help or why an individual will visit their doctor in some circumstances but not others[50]. Social theories and analysis of the social construction of gender provide explanations of how social influences, rather than biological differences, constrain men's and women's behavior[58]. Many gender theorists suggest that health care practices are gendered so that "doing" health reflects "doing" gender[72].

Health professionals themselves contribute to the gendered construction of health behavior. They criticize culturally idealized forms of masculinity for their part in men's reluctance to seek help but valorized or celebrated them at the same time. Men's reluctance to visit the doctor was accepted as amusing[73].

United States has provided more resources as well as economic and political power to men than to women[74]. Older widowers suffer social isolation because it was the wife who served as the connecting link between them and their family, friends, social groups, even the community in general. Men spent little time at home. There are dramatic differences between how men and women react to the death of a spouse. For men the feeling of loneliness can be summed up in one devastating sentence: "being lost without a compass"[75]. Advanced age and poor health were the major influences in remarriage[74]. The widowers who took care of their ill wives were considered as "Mr. Wonderful"[76]. Many adult men in Sweden have been doing poorly socioeconomically, somatically, psychologically and in overall healthfulness the past years. Positive associations among hopelessness, posttraumatic symptoms and burnout could be expected. Unemployment and retirement were associated with moderate/severe hopelessness[77].

Overweight, obesity and cancer mortality

The heaviest men and women [those with a body mass index (BMI) of at least 40] had death rates from all cancers that were 52% and 62% higher, respectively, than the rates in men and women of normal weight[78]. BMI is associated with a doubling of the risk of pancreatic cancer in both men and women[79]. There is no strong support for an association between BMI and prostate cancer[80]. Obesity and liver cancer; excess risk is higher among men than among women[81]. The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence of a cancer-preventive effect of avoidance of weight gain for cancers of the colon, breast (in postmenopausal women), endometrium, cervix, kidney (renal cell carcinoma), pancreas, liver, gastric cardia and esophagus (adenocarcinoma). Gallbladder cancer and high BMI have involved too few cases for the association to be evaluated in men[81]. Gout is the most common form of inflammatory arthritis in men affecting as many as 3.4 million men in the US. There is no strong support for an association between BMI and prostate cancer.

Osteoporosis continues to be an under-recognized problem in men and it goes untreated in the majority of men with fractures. One-third of all hip fractures worldwide occur in men and more men than women die in the year after a hip fracture with a mortality rate in men of up to 37.5%. The observation that the majority of fractures occur in men whose bone mineral density measurements are not in the osteoporotic range underscores the importance of factors other than bone mineral density (BMD) in determining the risk of fracture[82]. Exercise capacity is a more powerful predictor of mortality among men than other established risk factors for CVD[83].

Sexual and mental health was raised as particularly problematic for men seeking help. Unfriendly waiting rooms, difficult and judgmental receptionists, limited appointment times and doctor's attitudes were some of the reasons that men did not always discuss their real concerns and problems[84]. Men seem to get professional care at a later stage of their illness than women. There is less attention being paid to symptoms and to pain management[85]. Men as group are less likely to utilize the health care system than women. American men are less likely to carry health insurance, less likely to have seen a physician in the previous year and more likely to delay seeking health care than American women[86]. The health authorities in general ignore the fathers' involvement, interest and engagement in participating in prenatal courses and delivery[87].

Andropause

World population is aging rapidly. Elderly population ratio in Turkey is 6.8% and life expectancy at birth for men is 68 years[88]. Increasing elderly age group causes demographic

shift around the world. This global change in demographics draws attention of the medical world to elderly women and men. Now that men are living longer there is heightened interest about andropause.

Testosterone is the major hormone responsible in men for manly characteristics. However starting approximately at about age 30 testosterone levels drop about 10% every decade, which means about 1% every year[89]. Beside this change sex hormone binding globulin increases and binds more available hormone, which helps to end up with even less bioavailable circulating testosterone[90,91]. The term *late-onset hypogonadism* (LOH) describes this condition more accurately.

Men begin to experience some changes in his body somewhere between ages 40-60. This period which does not have any clear-cut demarcation is called andropause. The recognized hormones whose changes are thought to drive the clinical picture in andropause are primarily testosterone but there are other hormones responsible in the clinical picture of andropause[92].

LOH has been defined as low T levels and low to subnormal gonadotropin levels in connection with an array of physical, psychological and sexual symptoms[93]. Total testosterone level over 320 ng/dl is normal and lower than 200 ng/dl levels can be defined as hypogonadism[94]. Testosterone level at youth should also be taken into consideration when evaluating biochemical outcomes. In addition, response of muscles, brain and bones to low levels of testosterone is also important.

Andropause symptoms can be evaluated as physical, psychological and sexual[95].

There are many physical symptoms, which are familiar with aging, like muscle weakness, skin alterations, decrease in body hair[92].

Many of the psychological symptoms are also consistent with aging, like decreased intellectual capacity. There are studies reporting that verbal and visual memory and mental status improves with androgen therapy[95]. Since androgen deficiency is held responsible for cognitive decline, there are some small clinical trials reporting that low T levels has been detected prior to the onset of Alzheimer's disease and some report that T replacement improves cognitive function[96]. There is also increase in depression in men with low T levels, who met the LOH criteria[97,98]. Irritability, fatigue, altered sleep patterns are other psychological symptoms.

Sexual symptoms of andropause are an important point of interest. Both sexual desire and erectile quality decreases. Erectile dysfunction has been experienced by more than 1 men in 2 between ages 40-70[99].

Time of onset, speed of progression and degree of effect of andropause varies in different body systems and in different people. Prevalence of symptomatic LOH under age 60 is 7% whereas it is 20% over 60 years old[92].

The Future of Aging Male and Androgen Therapy

Advances in understanding aging processes and their consequences are leading to the development of therapies to slow or reverse adverse changes formerly considered to be "normal" aging and processes that underlie multiple age-related conditions[100-102].

The lack of a major, identifiable displacement in hormonal status, makes the characterization of age-normal male endocrine status particularly difficult. Testosterone and DHEA decline with age, whereas LH, FSH, and sex hormone-binding globulin (SHBG) rise with age. At least one important testosterone metabolite, dihydrotestosterone (DHT), apparently remains constant despite the decline of its precursor, androstanediol glucuronide (AAG); dehydroepiandrosterone (DHEA); DHEA sulfate (DHEAS); dihydrotestosterone (DHT); sex hormone-binding globulin (SHBG): MMAS, The Massachusetts Male Aging Study, a 10-yr prospective observational survey of health and aging in middle-aged men [103,104]. Natural testosterone is viewed as the best androgen for substitution in hypogonadal men. The reason behind the selection is that testosterone pro-hormone that can be converted to 5á-dihydrotestosterone (DHT) and 17-estradiol (E2) thus developing the full spectrum of testosterone activities in long-term substitution. The major goal of androgen substitution is to replace testosterone and the 5á-dihydrotestosterone (DHT) and 17-estradiol (E2) levels close to their physiological levels[105,106].

Little consensus exists among clinicians as to what constitutes a normal sex hormone profile for an aging male caused by the complex interrelations of the sex hormones with other hormone systems, with common chronic diseases of aging such as cancer, cardiovascular disease, diabetes, depression, hyperlipidemia, and arthritis, and with associated conditions and behavior such as obesity, sedentariness, nutritional deficiency, impotence, and frailty.

Androgen Replacement Therapy (ART) should have a good safety profile without adverse effects on the prostate, serum lipids, liver or respiratory function, and they must be convenient to use and patient-friendly, with a relative independence from medical services.

Replacement with unmodified testosterone is preferred, the dosage is arranged to maintain plasma testosterone in the physiological range over 24 hours of the day. The traditional injectable testosterone esters (testosterone enantate, testosterone cipionate, etc.) are inexpensive compared with newer forms of treatment but they do not meet the requirements.

Although the plasma DHT tends to be above normal with oral testosterone undecanoate, in a dose of two 40mg capsules (80mg) twice daily, it may provide plasma testosterone levels within the normal ranges in 80% of patients 95% of the time. Oral testosterone undecanoate dissolved in castor oil bypasses the liver via its lymphatic absorption. They may be suitable for the aging male with plasma testosterone levels indicating hypogonadism.

The mainstays of testosterone substitution are parenteral testosterone esters (testosterone enantate and testosterone cipionate) administered every 2–3 weeks. A major disadvantage is the strongly fluctuating levels of plasma testosterone, which are not in the physiological range at least 50% of the time. Also, the generated plasma E2 is usually supraphysiological[107]. A major improvement is parenteral testosterone undecanoate producing normal plasma levels of testosterone for 12 weeks, with normal plasma levels of DHT and E2 also.

Subcutaneous testosterone implants provide the patient, depending on the dose of implants, with normal plasma testosterone for 3–6 months. However, their use is

not widespread[108,109].

Transdermal ART: For two decades transdermal testosterone preparations have been available and have an attractive pharmacokinetic profile. Scrotal testosterone patches generate supraphysiological plasma DHT levels, which is not the case with the nonscrotal testosterone patches. Transdermal testosterone gel produces fewer skin irritations than the patches and offers greater flexibility in dosage. Oromucosal testosterone preparations have recently become available[107,110].

Transdermal ART with both scrotal and nonscrotal testosterone patch and the testosterone gel, testosterone implants and injectable testosterone undecanoate meet the above mentioned requirements. With a better understanding of the biological effects of testosterone in the various target organs and particularly regarding prostate, the goals of ART will be reformulated. Androgenic compounds with different degrees of tissue selectivity may find their place in ART [108,111-118].

Selective Androgen Receptor Modulators (SARMs) are a new class of Androgen Receptor (AR) Ligands. They can change the future of androgenic therapy. SARMs are expected to extend the clinical use of androgens for osteoporosis, muscle wasting, male contraception and diseases of the prostate. With improved pharmacokinetic characteristics and tissue-selective pharmacological activities, Studies with currently available SARMs will help to define the contributions of differential tissue distribution, tissue-specific expression of 5á-reductase, ligand-specific regulation of gene expression and androgen receptor interactions with tissue-specific coactivators, and lead to the expansion of selective anabolic therapies[119-121].

Testosterone replacement is usually of long duration and patient compliance is very important. Therefore, the patient must be involved in the selection of type of the testosterone type. Administration of testosterone to young individuals has almost no adverse effects. With increasing age the risk of adverse effects on the prostate, the cardiovascular system and erythropoiesis increases. Consequently, short-acting testosterone preparations are better for aging men. The underlying conditions that necessitate androgen replacement therapy are usually irreversible and a life-long ART is required. Patient compliance with life-long ART depends on convenient pharmaceutical formulations ensuring continuity of androgen replacement. The effects of androgens are much broader than subserving male sexual functionning, including those on bone, muscle, cardiovascular functions and brain and, consequently, androgens have a profound impact on quality of life[122,123].

The benefits of ART are clear, but the delivery of testosterone to hypogonadal men in a way that approximates normal levels and patterns still poses a therapeutic challenge. Developing an ideal form ART requires much effort. General agreements about such an ART are[124]:

(i). a delivery of the physiological amount of testosterone (3–10 mg/ day);

(ii). consistent levels of testosterone, 5-dihydrotestosterone (DHT) and 17-estradiol (E2) within normal physiological ranges;

(iii). similar circadian patterns of hormone levels as in healthy young men;

(iv). a good safety profile without adverse effects on the prostate, serum lipids, liver or respiratory function; and

(v). convenience in usage, patient-friendly, with a relative independence medical services.

In aging men, for instance, androgen replacement aims to produce physiological anabolic effects, but a serious concern is prostate safety. It is possible that a synthetic androgen could be developed, for example, which is safer for the prostate than natural testosterone. Further studies are required to decide if there are drugs androgenic action which provide beneficial androgenic effects while still controlling the risks of replacement.

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