Men's Health Journal. 2019; 3(1): e13

OPEN ACCESS

REVIEW ARTICLE

Andropause in Iranian Men: Related Factors and Consequences; a Systematic Review

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Received: November 2019; Accepted: November 2019; Published online: December 2019

Abstract: **Introduction:** Andropause is a syndrome with a slow progression that is associated with androgen deficiency in older men. This study aimed to collect all scientific data about the factors that cause the occurrence of andropause in Iranian men as well as the aspects of life which can be affected by this disorder. **Materials and Methods:** Searching was conducted in international databases including MedLine, Scopus, Web of Science, ProQuest, and national database (SID) from inception until December 2019. Retrieved studies were reviewed by two researchers independently and selected studies were summarized in a table. **Results:** Finally, 21 related studies were included and summarized information showed that andropause can be negatively affected by age, lower testosterone levels, smoking, lower economic status, lower educational level, and poor employment status. Some studies have also implied that there is a significant correlation between andropause and quality of life, sleep quality, depression, anxiety, marital dissatisfaction, urinary incontinence, coronary heart disease, and metabolic syndrome. **Conclusion:** According to the collected data in this present study, Iranian studies have covered a wide variety of complications and related factors in the field of andropause but, we still lake some studies about other aspects of andropause such as musculoskeletal impairment, erectile dysfunction, memory and cognitive disorders, skin and hair disorders, decreased libido, and other mood disorders.

Keywords: Andropause; Late-onset hypogonadism; Systematic Review; Testosterone

Cite this article as: Aliakbari F, Allameh F, Tavakoli A, Ajorloo M, Hosseini M A, Shojaeefar E. Andropause in Iranian Men: Related Factors and Consequences; a Systematic Review. Mens Health J. 2019; 3(1): e13.

1. Introduction

Andropause is a series of geriatric procedures that is physically pretty similar to menopause in women and occurs in ages above 45. The amount of protein attaching to male sex hormone (SHBG) increased in middle ages men, which reduces free testosterone [1]. This procedure sometimes occurs prematurely for reasons other than the normal aging process such as cardiovascular diseases, long-term use of some medications, stress, depression, poor sleep quality, diabetes, metabolic syndromes, obesity, and alcoholism, all of which impact testosterone production [1].

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Contrary to women's menopause, men do not face infertility in andropause; however, their success in fertility drops significantly. The most prevalent signs of andropause in the literature are fatigue, impatience, depression, anger, increased irritability, reduced sexual activity, reduced muscle mass, flushing, memory impairment, nocturia, hair loss, constipation, and bone pain [2]. This syndrome has a slow progression that is associated with androgen deficiency in older men (age > 50 years) [3, 4]. There are several terms for this syndrome including male menopause, androclise, androgen decline in the aging male (ADAM), aging male syndrome (AMS), late-onset hypogonadism (LOH) [5]. Andropause can also occur in men who have lost their sexual function, due to accidents or advanced prostate treatment. The rate of decrease in testosterone levels varies in different peoples. Decreased testosterone or sperm production is related to male hypogonadism [6, 7] which is caused by androgen deficiency and can adversely affect multiple organ function and quality of life [6,

8].

Serum testosterone levels decrease with aging in men at a rate of 1% per year. This decrease is associated with changes in body function, declined physical energy, and muscle strength. Andropause is characterized by the following symptoms such as nervousness, reduced potency and libido, fatigue, depression, memory, and sleep problems [9]. Ninety-eight percent of testosterone in plasma is combined with proteins (65% to sex hormone-binding globulin (SHBG) and 33% to albumin) [2] and only 2% of testosterone is free in serum. Smoking, obesity, alcohol use, lifestyle, and various chronic illness are the factors that can be effective in testosterone decline [10, 11]. Obesity reduces the total testosterone and SHBG levels [11]. Job stress is a major factor related to andropause symptoms for male workers. Studies indicated that a high level of job stress is associated with andropause symptoms in men [2].

Decreased free testosterone level is the least concerning issue among all parameters. Andropause without testosterone deficiency has also been reported in men so the causes of andropause are not clear [12]. We focused on this topic to figure out all effective factors in the occurrence of andropause and also to know how andropause affects aspects of Iranian men's life and health and also to show where we have the research gap comparing to the studies from around the world.

2. Material and Methods

This study aimed to collect all scientific data about factors that cause the occurrence of andropause in Iranian men as well as aspects of life that can be affected by this disorder. Accordingly, this selected title was considered to include all types of studies (cross-sectional, prospective, and Cohort studies, etc.) reporting factors and outcomes of andropause in the Iranian male population. Considering the following keywords: "Andropause", "male menopause", "Testosterone deficiency", "late-onset hypogonadism", "hypogonadism" and "Iran", electronic searching was conducted in international databases including MedLine, Scopus, Web of Science, ProQuest, and national scientific information database (SID) from inception until December 2019. No language restriction defined and eligible studies could have been published in either English or Farsi. Exclusion criteria were non-Iranian participants and studies about knowledge and attitude in this field and also if the testosterone deficiency had a congenital origin. The Process of selecting articles completed by two independent researchers. Extracted data entered into a table which included bibliographic information of studies (author's name, publication year), study type and design (participants, conducted tests or questionnaire, intervention, grouping and follow up duration), and the main study achievements about factors involved in and affected by andropause. Due to the wide variety of reported data across studies, the meta-analysis was not applicable. Finally, the overall statements of the included studies were compared and discussed to obtain a comprehensive conclusion.

3. Results

At the initial searching phase, 243 articles were retrieved. the Screening was initially done on study titles which led to the exclusion of 195 articles. Additional 27 articles were excluded due to studying different target groups, non-Iranian, knowledge, and attitude about andropause and also if they were not original studies or no full text available. Finally, 21 original studies met the inclusion criteria for this systematic review (Figure 1).

Based on reviewed studies which were summarized in table 1, several factors contribute to the occurrence of andropause including age, lower testosterone levels, smoking, lower economic status, lower educational level, and poor employment status. There were also some data about factors that affect the gonadal function and cause hypogonadism including age, HIV, thalassemia, radiotherapy, hypertension, smoking, methadone therapy, and higher duration of diabetes (Table 2).

Some studies have also implied that there is a significant correlation between andropause and quality of life, sleep quality, depression, anxiety, marital dissatisfaction, urinary incontinence, coronary heart disease, and metabolic syndrome. Some studies also demonstrated the correlation of hypogonadism or gonadal dysfunction with BMI, prolactin, depression, FBS, HA1C, hyperlipidemia, waist circumference, hemoglobin, and LH (Table 3).

There were only three interventions that reported significant improvement of the andropause symptoms using testosterone replacement therapy (TRT) and an educational package.

4. Discussion

Given the title of the present study which indicates that it aims to study andropause in Iranian men as well as its reasons and consequences, we will also proceed to study the clinical symptoms of andropause syndrome. According to a holistic study, these consequences can be divided into the following main categories:

1. Physical consequences such as abdominal obesity, reduced muscle mass, reduced mineral density in bones, decreased body hair, and changes in skin
2. Mental consequences including depression, impairment of the cognitive function monitoring center, and increased tiredness
3. Sexual function consequences such as reduced sexual

drive, reduced sexual function quality, and erectile dysfunction [24]

Clear signs of men entering their andropause period manifest in the older male population. A Korean review study reported that 64.4% of men aged 45 to 70 might suffer from andropause syndrome, the most prevalent symptom of which is erectile dysfunction which manifests in 71% of cases and has the highest share among other symptoms. This study also pointed out that andropause is a biochemical clinical syndrome depending on age which manifests due to testosterone shortage, and patients experience a considerable drop in the quality of life as well as complications in bones, fat tissue, muscles, brain, and hematopoiesis mechanisms. In this regard, decreased testosterone in men aged over 50 generally resulted in symptoms such as lack of concentration, nervousness, memory impairment, depression, sleep deprivation, low energy, a general feeling of sickness, reduced libido, erectile dysfunction, Joint and bone pain, lower general strength, increased BMI, and obesity [25].

Another study considered erectile dysfunction to be the most important complication due to andropause, which was observed in 38% of the study population [26] The authors of this review suggested to assess erectile dysfunction prevalence in Iranian men and also in the subgroup of late-onset hypogonadism in more epidemiologic studies.

Akmal Taher conducted a study on 501 people aged 40 to 90. The author examined participant's primary data such as age, education, occupation, income, marital status, and sexual relationships to diagnose andropause and its intensity, and reported that 153 people out of the 499 participants suffered from andropause that is equal to 70.94% of the study population [27].

In a study, from 193 participants (54%) suffered from mild andropause, 138 participants (38%) suffered from moderate andropause, and only 23 participants (6.5%) suffered from severe andropause. It was also evident that andropause prevalence had a positive relationship with age [28]. This finding is similar to our endemic data.

Another population study focused on the manifestation of andropause reported symptoms such as mood disorders, nervous irritability, severe depression, memory impairment, severe fatigue, stress management failure, and a feeling of disgust towards activities that used to be pleasurable for the patient [29] This study indicated that 42% of the participants suffered from depression and its relevant disorders. Other participants experienced mood disorders. Psychologists believe that andropause is a period when men comprehend their lives as a whole and not as a series of their actions, and tend to experience a sense of underdevelopment [30]. These data are consistent with our national documents but more detailed statistics are needed.

A study conducted by Bechtz et al. in terms of admission criteria revealed the following: reduced libido in 91% of participants, a low energy level in 89%, erectile dysfunction in 77%, severe memory impairment in 77%, hair loss in 70%, irritability in 68%, reduced endurance in 66%, and performance dysfunction in 51% of men. They also showed that 21% of men aged 55-59, 26% of men aged 60-69, and 31% of men aged 70-89 suffered from reduced testosterone levels [31].

Another review pointed out that reduced testosterone levels accompanied decreased libido in 12%, erectile dysfunction in 16%, and osteoporosis in 1% of men. This review revealed that Middle-aged men experience a variety of symptoms, such as sexual and erectile dysfunction, reduced libido, poor sleep quality, mood swings, and low motivation. The reduced hormone concentration is gradual so the symptoms manifest gradually as well [32].

A report published in the New England Journal of Medicine offers other viewpoints. A biochemical, clinical experiment conducted on 3,369 men aged 40-79 indicated that symptoms such as sexual manifestations including a lower number of sexual intercourse and impaired ability to engage in strenuous activity such as running, lifting heavy objects, performing heavy physical exercises, walking more than 10 km, bending on the knee, and psychological symptoms such as low energy, sadness, grief, and fatigue have no significant relationship, while symptoms such as changes in sleep patterns, concentration loss, feeling worthless, nervousness, anxiety, and difficulty getting up from the sitting position are associated with andropause [33]. Our results showed a correlation of andropause with sleep quality and anxiety too.

Another study also points out that testosterone decreases by 1% as a result of aging, and the reduced testosterone level is more pronounced due to the globulin attached to the sexual hormone The extent of hormonal changes is different from person to person and can be associated with various factors such as diseases, obesity, and medication. Reduced testosterone concentration might result in impaired memory, verbal function, and visual function, and might impact multiple other functions such as a wide range of mood disorders, metabolic disorders, osteoporosis, and cognitive decline [34].

5. Conclusion

According to the collected data in this present study, it is recommended to conduct more comprehensive studies about causes and complications caused by andropause in middle-aged men that didn't mention in Iranian studies. Indeed, Iranian studies have covered a wide variety of complications and related factors in the field of andropause but, we still lake some studies about other aspects of andropause such as musculoskeletal impairment, erectile dysfunction, memory and cognitive disorders, skin and hair disorders, decreased libido, and other mood disorders.

6. Appendix

6.1. Acknowledgements

None.

6.2. Authors Contributions

All the authors have the same contribution.

6.3. Funding Support

None.

6.4. Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Table 1: Summary of included studies about factors that affect or affected by andropause. (Continuous)

First Author [reference]	Study design (questionnaire, intervention, sample size, age, place)	Study type	Maine finding
Najafabady, 2013 [3]	ADAM and serum levels of free and total testosterone in 90 male, >40 y, university staffs	cross-sectional	No significant relationship between participants with and without andropause symptoms regarding age, BMI, blood pressure, income or free and total testosterone
Sofimajidpour, 2015 [5]	ADAM and serum testosterone in 80 men, >50 y, before and after daily 40mg testosterone for 6 m	Before-after study.	Significant decrease in andropaused men form 100% to 87.5, 55 and 0 at baseline, 1, 3, 6 months after treatment respectively
Afsharnia, 2016 [10]	SF-36 & AMS in 80 men, 40-60 y, TUMS staff.	Cross-sectional	Andropause causes low QOL and there was a significant relationship between age and Andropause
Hakimi,2019[13]	Socio-demographic & MASSQ in 264 andropausal men, mean age 58.8, Tabriz.	Cross-sectional	Unemployment, retirement, marital dissatisfaction, being a tenant, and having no academic education were predictors of severe andropause symptoms.
Khosravi,2014[4]	AMS & PHQ-2 and 9 were used to screen depression & MET & multi-sectoral (about demographic and fertility) in 521 men, 45-65y from blood donation organization	Cross-sectional	There was significant correlation between depression and andropause (r=0.48)
Mousavi,2018[11]	Socio-demographic and health status & MASSQ & SF-12 in 393 men, 40-85 y, urban health care center in Ilam	Cross-sectional	Men with higher andropausal symptoms had lower QOL, predictors of andropause were: higher age, lower education, depression, coronary heart disease, and urinary incontinence
Mousavi,2018[14]	ADAM in 600men 40-65y, health centers in Arak	Cross-sectional	There was a significant relationship between age and Andropause and sexual life quality
AliAkbari,2019[15]	Socio-demographic (GHQ) and ADAM & psychological health in patients with psychology sign of andropause and patients with the clinical diagnosis of andropause in 150 men, 45-65y, staff of TUMS.	Casual-comparative	Patients with laboratory diagnosis of andropause had severe depression and anxiety
Samipoor,2017[16]	Demographic & AMS, 140men, >40 y, health center in Rasht	Cross-sectional	Men over age 40 had experienced symptoms of andropause, there is a significant positive correlation between BMI and Andropause.
Madani ,2011[9]	Demographic, history of drug usage, history of surgeries and history of neurologic, psychogenic, endocrine, cardiovascular and urologic diseases & NCEP-ATP III criteria (for metabolic syndrome) & Morning serum FT in 241men with ED, mean age 50		The relative frequency of metabolic syndrome and testosterone deficiency in men with ED seems to be significant and it can cause cardiovascular disease. So ED can be a sign of a need for medical intervention.

Table 1: Summary of included studies about factors that affect or affected by andropause. (Continuous)

First Author [reference]	Study design (questionnaire, intervention, sample size, age, place)	Study type	Maine finding
Afsharnia 2017[8]	SF-36 & AMS in 80 men, 40-60y, TUMS stuffs.	Quasi-experimental	The computer-based educational package has a positive effect on QOL and reduction of hypogonadism symptoms
Afsharnia 2019[6]	A demographic questionnaire and then the AMS & diagnosis of male hypogonadism by the urologist in 80men 40-60y, TUMS stuffs.	Cross-sectional	There was a significant association between age and severity of hypogonadism and also between the economic status, cigarette consumption, hours of sleep, and the severity of hypogonadism symptoms.
Ahmadloo,2010[17]	Pelvic radiotherapy 50-Gy radiation & 2Gy per fraction 5days a week and 5-FU-based chemotherapy & testis dosimetry twice during study & blood samples for LH, FSH, and Testosterone were taken 3 times: before, during and 4 to 6 week after study in 40 men with Rectal adenocarcinoma, Mean age 58.	Cross-sectional	There was a significant increase of FSH, LH, and decrease of Testosterone after radiation and risk for testicular damage, hypogonadism, and infertility
Aminilari,2012[12]	Socio-demographic & BMSFI (for assessing sexual function) & Beck Depression Inventory-II & blood sample for total and free testosterone in 278 men with HIV, mean age 37y	Cross-sectional	68% had hypogonadism, 74% minimal and 68% moderate to severe depression and they have low levels of testosterone. There was a direct association between depression and gonadal function. There was a negative association between gonadal function and methadone therapy
Faramarzia,2014[18]	Socio-demographic & morning serum for FT, TT, LH, FSH, and prolactin in 278 men with HIV positive mean age 37 y	Cross-sectional	The prevalence of hypogonadism in HIV positive patients was high (62.8% based on FT). hypogonadism was positively associated to PRL (OR: 1.18), age and methadone use (OR:1.47) and negatively with BMI (0.88), LH (OR = 0.91), HGB (OR = 0.788). but had no significant association with HAART, smoking, hepatitis or reaching the AIDS stage.
Heydari 2014[7]	IIEF & TT, LH, PRL and TSH (only if LH was low) before and 3 W after TRT (A single dose of 250 mg (IM) testosterone), in 48 men with ED and LOH symptoms, mean age 53	Quasi-experimental	94% of patients got a significant improvement in libido, QOL, and IIEF. LH decreased significantly after TRT, but the testosterone level had no change.
Karimi,2012[19]	LH, FSH, PRL, testosterone, and estradiol in 75 men with Beta-Thalassemia under treatment of HU 8-15mg/kg/day at least 5 years, in comparison with 31 patients without HU. mean age 22.7, in southern Iran.	Case-control	There was no significant difference in the level of gonadal hormone between patients with or without HU.

Table 1: Summary of included studies about factors that affect or affected by andropause.

First Author [reference]	Study design (questionnaire, intervention, sample size, age, place)	Study type	Maine finding
Mirzaei,2012[20]	TT & SHBG & ADAM in 325 diabetics men >30 y, Isfahan	Cross-sectional	Based on TT and cBT Prevalence of borderline hypogonadism was 9.9% and 36%, respectively. TT was negatively correlated with BMI and triglyceride. Hypogonadism (TT ≤12 nmol/l) was not correlated with obesity, smoking, age, duration of diabetes, blood pressure, and HbA1c.
Sadat Hosseini,2019[21]	ADAM & FT & demographic & lipid and glycemic control & BMI, blood pressure & SF-36 in 2 groups (67 diabetes men without hypogonadism and 93 diabetes men with hypogonadism, mean age 53-59	Case- control	Dyslipidemia, FBS and HbA1c, waist circumference and, BMI were significantly higher and QOL was lower in hypogonadal patients compared with patients without hypogonadism.
Samipoor 2017[22]	AMS & FT & TT& FSH & LH in140 men >40y, GUMS	Cross-sectional	73% of men had LOH symptoms among them 3.8% had low FT and 33% had low borderline TT. The LH and FSH levels increased with age. There was a significant association between LOH score >34 with age (OR:1.05), BMI (OR: 1.15), smoking (OR: 2.2). Self-employed (OR:4.38) and employees (OR: 3.14) had higher odds in comparison with workers.
Sayehmiri,2016[23]	16 document about the prevalence of Hypogonadism in Thalassemic patients, Mean age 17	Meta-analysis	There was a high prevalence of hypogonadism (49%) in men with Thalassemia Major. The highest prevalence was in Bushehr and the lowest in Zanjan

ADAM: Androgen Decline in the Aging Male, TUMS: Tehran University of Medical Science, AMS: Aging Male Scales,
y: year, M: month. MASSQ: male andropause symptoms self-assessment questionnaire. PHQ: Patient Health Questionnaires,
MET: Metabolic Equivalent of Task, SF-12: 12-item Short Form Health Survey,
NCEP-ATPIII: National Cholesterol Education Program- Adult Treatment Panel III, ED: erectile dysfunction,
SF-36: 36-item short form health survey, QOL: Quality of life, Gy: Gray, FU: Fluorouracil,
LH: Luteinizing Hormone, FSH: Follicle-Stimulating Hormone, BMSFI: Brief Male Sexual Function Inventory,
TT: Total testosterone, FT: free testosterone, HGB: Hemoglobin, PRL: Prolactin, HAART: highly active antiretroviral therapy,
AIDS: Acquired immunodeficiency virus, TSH: Thyroid stimulating hormone, IIEF: International Index of Erectile Function,
TRT: testosterone replacement therapy, LOH: late-onset hypogonadism, HU: Hydroxyurea,
cBT: Calculated bioavailability of testosterone. LDL: Low-density lipoprotein, BMI: Body mass index,
SHBG: Sex hormone binding globulin, GUMS: Guilan University of Medical Science,
GHQ: General health questionnaire, HbA1c: Hemoglobin A1C, FBS: Fasting Blood Sugar.

Table 2: Factors that contribute to the occurrence of andropause or affects the gonadal function.

	The number of studies mentioned significant (+) or no significant (–) effect	
Factor	**Andropause or LOH**	**Hypogonadism or gonadal dysfunction**
Age	+ + + + + + –	+ + +
Lower Testosterone level	+ + + + –	NR
Smoking	+ +	+ –
Lower economic status	+ + –	NR
Lower educational level	+ +	NR
Poor employment status	+ + +	NR
Methadone therapy	NR	+ +
HIV	NR	+
Thalassemia	NR	+
Radiotherapy	NR	+
Hypertension	–	+
Higher duration of diabetes	NR	+
highly active antiretroviral therapy	NR	–
Hepatitis	NR	–
AIDS	NR	–
Hydroxyurea	NR	–

NR: Not Reported

Table 3: Factors that have correlation with andropause or hypogonadism.

Factor	**Number of studies mentioned positive (+) or negative (–) correlation**	
	Andropaus or LOH	**Hypogonadism or gonadal dysfunction**
Quality of life	– – –	–
Sleep quality	–	NR
BMI	+ +	– + +
Depression	+ +	+
Anxiety	+	NR
marital dissatisfaction	+ +	NR
urinary incontinence	+	NR
coronary heart disease	+	NR
metabolic syndrome	+	NR
prolactin	NR	+
FBS	NR	+
HbA1C	NR	+
hyperlipidemia	NR	+
Waist circumference	NR	+
Hemoglobin	NR	–
LH	NR	–

BMI: Body Mass Index
FBS: Fasting Blood Sugar
LH: Luteinizing Hormone

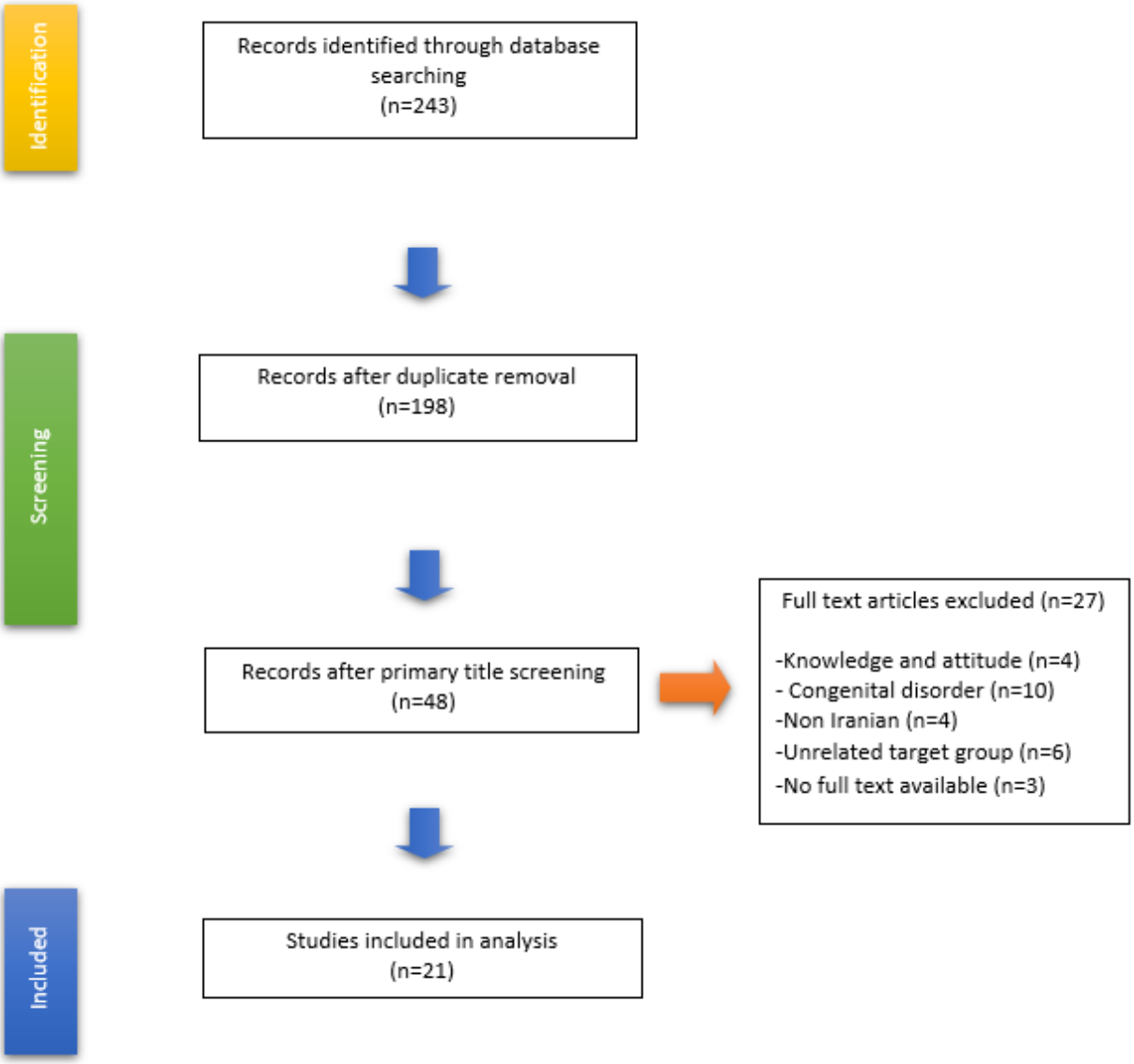

Figure 1: PRISMA Flow diagram of studies on factors involved in and affected by Andropause in Iranian men.