

Relative Testosterone Deficiency in Older Men: Clinical Definition and Presentation

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The increased longevity observed in many communities worldwide has created a need to foster healthy aging. Devising safe and effective medical approaches that prolong healthy, independent, and enjoyable living is therefore a priority for health care providers. Androgen replacement therapy for older men holds promise in this regard, because systemic levels of testosterone fall by 1% to 2% each year, creating a state of relative (compared with young men) androgen deficiency [1,2]. Furthermore, many aspects of aging resemble features of organic androgen deficiency in younger men in whom testosterone replacement is an accepted therapy and widely regarded as safe, affordable, and effective [3,4] (Table 1).

In contrast, androgen replacement therapy in older men remains controversial for numerous reasons [5,6]. First, rigorous data confirming age-specific benefits over potential long-term adverse effects are limited. Second,

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Table 1

Clinical features of androgen deficiency and comparison of effect of androgen administration in organic androgen deficiency and aging

Criteria	Features	Reversal by androgen	
		Organic androgen deficiency	Aging
Muscle mass	↓	Yes	Yes
Muscular strength	↓	Yes	Yes
Fat mass	↑	Yes	Yes
Physical function	↓	Yes	?
Bone density	↓	Yes	Yes
Hair/skin	↓	Yes	?
Cognition/mood	↓	Yes	?
Libido	↓	Yes	?
Quality of life	↓	Yes	?

many older men may have serum testosterone levels that are only modestly below the young healthy male range, and thus the chemical abnormality may not be sufficient to warrant replacement. Third, concerns about risk-to-benefit ratios that are age-specific (ie, prostate and cardiovascular disease) remain in the critiques of many clinicians. Finally, many of the clinical features attributed to relative androgen deficiency are subtle and nonspecific and conceivably could be caused by many etiologies, including other hormonal deficiencies (particularly growth hormone and possibly, estradiol), mitochondrial dysfunction, increased cytokines, and oxidative stress. This confounds the clinical presentation of relative testosterone deficiency. For these reasons, the efficacy and safety of androgen therapy in older men will remain undefined until additional data from adequately powered randomized placebo-controlled studies become available to validate or refute the clinical significance and interventional potential for this putative syndrome.

Relative androgen deficiency in older men: the questions

Does it exist?

There are overwhelming indirect data showing that relative androgen deficiency exists and that the merits and risks of replacement therapy are worthy of consideration. Aging is associated with specific and multiple alterations throughout the entire hypothalamo–pituitary testicular axis. Such changes in luteinizing hormone (LH) and testosterone secretion characteristics and their integrative feedforward and feedback regulation [7] strongly implicate the relevance of testicular axis alterations in the pathogenesis of a subtle clinical syndrome. These changes associated with aging orchestrate the irrefutable decline in systemic testosterone exposure (measured as total, free or bioavailable testosterone) with age that has been confirmed in many representative longitudinal and large cross-sectional cohorts worldwide (see Liu and

colleagues elsewhere in this issue). This decline likely explains at least some of the symptoms and signs such as lethargy, sexual dysfunction, decreased muscle, osteopenia, and increased fat commonly observed in older men. Relative testosterone deficiency in older men? The term adequately describes the phenomenon that serum testosterone concentrations fall with age. Multiple alternatives such as viropause, partial androgen deficiency of aging men (PADAM), androgen deficiency of aging men (ADAM), senile hypogonadism, and, most recently, late-onset hypogonadism have been used to describe this same clinical syndrome. Other terms such as andropause or male menopause may be less satisfactory, because they draw an inappropriate analogy with the female menopause, which in contrast is a clear-cut and well-defined clinical syndrome associated with the cessation of menses. The plethora of so many descriptive terms may reflect the ill-defined nature of any putative clinical syndrome of age-specific relative androgen deficiency.

Ideally, the clinical syndrome (symptoms, signs, and simple laboratory investigations) should identify a group of older men who are more likely to favorably respond to androgen therapy (ie, have more beneficial effects or fewer adverse effects), or predict a group of men who are likely to undergo accelerated functional decline. In either group, testosterone (or some other adjunctive therapies) may benefit the patient. Unfortunately, no such definition is available. Although the degree of androgen deficiency, as assessed by baseline systemic testosterone exposure, is a predictor of androgen responsiveness in older men [8], the utility of defining a syndrome [9,10] that simply correlates with low serum testosterone concentrations is of limited usefulness given the ease with which blood can be obtained and analyzed. Any such definition should include a serum concentration testosterone or specific testosterone fraction measurement [5,11–13], and a threshold level for the chemical diagnosis is required. Estimates of prevalence rates based on testosterone concentrations are premature given the uncertain response relationship between serum testosterone concentrations and any clinical syndrome [2,14,15].

Best practice guidelines provide a definition based on low serum concentrations of total testosterone or its non-sex hormone-binding globulin (SHBG) bound component (ie, free or bioavailable testosterone) in combination with a compatible clinical picture [5,11–13]. Such a definition is premised upon extrapolating the clinical syndrome of organic androgen deficiency of young men into the older population. Which testosterone cut-off to employ (using which testosterone measurement) and which complex of symptoms and signs define the disorder remain controversial, however. Furthermore, the extrapolation of clinical symptomatology in particular is confounded by differing comorbidities.

Should relative androgen deficiency of older men be treated?

Considerable evidence shows that hypogonadism in younger men responds favorably in many distinct clinical domains to testosterone treatment

[3,4]. The possibility that older men may fail to respond or be less responsive to testosterone treatment compared with young men has been highlighted by some investigators. To the contrary, recent data have shown equivalent increases in muscular mass and strength and comparable decreases in fat mass in response to short-term testosterone treatment irrespective of age [16]. These data, showing no age-associated worsening in testosterone responsiveness strongly imply that the age-related relative decrease in systemic testosterone concentration has real and reversible effects on skeletal muscle and adipose tissue and inferentially suggest similar relationships with other androgen-responsive tissues. Because muscular mass and strength are known determinants of physical function, disability, and quality of life, these data suggest that these effects of androgen replacement therapy in the older male may have other widespread nonmuscular effects. Thus androgens could improve physical functioning by preventing the frailty, falls, and fractures in older men that mar quality of life and threaten independent living. The definitive demonstration of functional improvement and decreased morbidity and mortality of testosterone treatment of age-related androgen deficiency are awaited.

Even if testosterone treatment is effective in older men, this may be negated by increased risks. The speculation that older men are more prone to adverse effects of testosterone treatment (in particular prostate disease, raised hematocrit, and fluid retention) has been confirmed directly [16]. It may be that a clinical syndrome of relative androgen deficiency exists, but treating all older men nonselectively with androgens could cause more harm than good. This is a potential problem for many therapeutic interventions and can be solved partly by vigilant monitoring and dose titration. Also, combining interventional strategies such as appropriate exercise with other anabolic agents may enhance effect and allow lower dosing.

Putative clinical definition of relative androgen deficiency in older men

Testosterone cutoff

At present, there are only limited data to show that a particular testosterone cutoff level separates older men by testosterone responsiveness or risk of disability. This is in stark contrast with well-demarcated cardiovascular risk-defined partition levels for diastolic blood pressure [17] or efficacy-defined division levels for blood glucose control [18]. Epidemiologic information linking chemical levels and symptom complex is accumulating slowly [19–21], and available data suggest a linear rather than bimodal relationship [8]. More information is needed [6]. Until this occurs, the segregation level of serum testosterone for diagnosing relative testosterone deficiency in older men has been defined statistically using normative ranges obtained from healthy young men. In such a population, the 95% confidence interval of serum total testosterone ranges from 300 to 1000 ng/dL (10 to 35 nmol/L),

provided that blood is sampled in the morning. In other words, 2.5% of all young men have blood concentrations below 300 ng/dL. Given the uncertainty of androgen therapy in older men, however, a more stringent 98% confidence interval may be applied, which corresponds to a blood testosterone concentration of about 250 ng/dL (8.7 nmol/L). Approximately 1% of healthy young men will have a serum testosterone concentration of less than 250 ng/dL. Such a threshold defining male hypogonadism has been adopted almost universally throughout the world [5,11–13]. As an example, the United States-based Endocrine Society has made the following recommendations [12]:

“If the serum testosterone level is above 350 ng/dL (12.1 nmol/L), then most likely the man does not have relative androgen deficiency. Values in between 250 and 350 ng/mL warrant a repeat serum level and further assessment of the unbound testosterone measured as free testosterone using equilibrium dialysis or ultracentrifugation to separate the free steroid from testosterone bound to proteins. If the testosterone levels are below 250 ng/dL on repeated samples, then the patient is likely androgen-deficient.”

Non-SHBG-bound (bioavailable) testosterone, which comprises the free and albumin-bound fractions, can be measured directly after ammonium sulfate precipitation. Either free or non-SHBG-bound testosterone can be calculated from concentration of total testosterone, and SHBG can be measured usually by immunoassays using the law of mass action (formula available at <http://www.issam.ch>). Bioavailable or free testosterone may help clarify the clinical picture in men with symptoms or signs suggestive of androgen deficiency and borderline total testosterone concentrations. Nevertheless, how androgen deficiency is defined and confirmed by which testosterone measurement remains unresolved, because empirical validation of these measures against independent biologic markers of androgen action in man is lacking [22].

Compatible clinical presentation

In younger men with organic androgen deficiency, commonly self-reported symptoms include lack of energy, diminished libido, erectile dysfunction, loss of motivation, cantankerous mood, sleepiness after lunch, and inability to concentrate [23]. Other symptoms such as hot flushes, slowed beard growth, and muscular aches also have been reported, but less frequently. These symptoms are putative markers of relative testosterone deficiency in older men, and variations thereof have been used both in the Androgen Deficiency in Aging Males (ADAM) and Aging Males' Symptoms (AMS) scale questionnaires (Box 1 and Fig. 1) [10,24–26]. The development of these questionnaires reflects two differing approaches to defining the presumptive clinical syndrome. The ADAM questionnaire was a screening questionnaire validated primarily against serum testosterone concentrations, and hence, it

Box 1. Androgen deficiency in aging males questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost weight?
5. Have you noticed a decreased enjoyment of life?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

A positive response is a yes answer to questions 1, 7, or any three other questions.

Modified from Morley JE, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism* 2000;49(9):1239–42; with permission.

can be viewed as a noninvasive method to screen for this outcome. The AMS questionnaire in contrast was not developed as a screening test for low testosterone concentrations, and it has not been compared against serum testosterone concentrations. Instead, it was designed as a quality-of-life questionnaire, for which population-based normative data derived from large samples from many different countries have been collected, and internal reliability and psychologic, somatic, and sexual subscale agreement have been verified [25]. Each component of the AMS (psychologic, somatic, and sexual symptomatology) has been shown in a limited unblinded study to improve with testosterone administration in older men [26]. In this study, however, only 40% of subjects enrolled were over the age of 60; placebo controls were not included in the study design, and the treatment was for only 3 months.

Sexual symptoms

Diminished sexual function is an important feature of organic androgen deficiency, and it universally is included as part of the clinical definition of relative age-dependent androgen deficiency [9,10,25]. The usefulness of this criterion in the aging male, however, is limited, because both components of sexual dysfunction (erectile dysfunction and reduced libido) occur commonly with increasing age, as demonstrated in numerous representative population-based studies (n = 28,000 men) [27–37]. Furthermore, this decline is unlikely to be related solely to the modest declines observed with age,

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".					
Symptoms:	none	mild	moderate	severe	Extremely severe
	1	2	3	4	5
1. Decline in your feeling of general well-being (general state of health, subjective feeling).....					
2. Joint pain and muscular ache (lower back pain, joint pain, pain in a limb, general back ache).....					
3. Excessive sweating (unexpected/sudden episodes of sweating, hot flushes independent of strain).....					
4. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)					
5. Increased need for sleep, often feeling tired					
6. Irritability (feeling aggressive, easily upset about little things, moody).....					
7. Nervousness (inner tension, restlessness, feeling fidgety).....					
8. Anxiety (feeling panicky).....					
9. Physical exhaustion/lacking vitality (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities).....					
10. Decrease in muscular strength (feeling of weakness).....					
11. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use).....					
12. Feeling that you have passed your peak					
13. Feeling burnt out, having hit rock-bottom					
14. Decrease in beard growth					
15. Decrease in ability/frequency to perform sexually					
16. Decrease in the number of morning erections					
17. Decrease in sexual desire/libido (lacking pleasure in sex, lacking desire for sexual intercourse).....					
Have you got any other major symptoms?	Yes...	No ...			
If Yes, please describe: _____					

Fig. 1. Aging males symptoms scale questionnaire. (Modified from Moore C, et al. The aging males' symptoms scale (AMS) as outcome measure for treatment of androgen deficiency. Eur Urol 2004;46(1):85; with permission.)

because the blood testosterone threshold for maintaining male sexual function is low [16,38,39]. The inability of serum testosterone to fully predict sexual dysfunction is illustrated further by analysis of a large twin database that showed that nonheritable factors account for no more than 70% of the variance in erectile dysfunction [40].

Nevertheless, primarily libido, and secondarily erectile function, are testosterone-sensitive parameters [38,39,41–43]. Although testosterone-sensitive, erectile dysfunction in older men is multi-factorial in origin and cannot often be explained simply by organic androgen deficiency [44]. Hence the discriminatory utility of screening men with sexual dysfunction for relative androgen

deficiency is limited, and positive identification is likely to be confined to men who are more severely androgen deficient.

Somatic symptoms

Somatic features related to symptoms of decreased muscular strength, fatigue, and energy; clinical signs of reduced lean mass and increased adiposity; and reduced beard growth are all features of organic androgen deficiency. These characteristics also have been incorporated universally into the clinical definition of age-related relative androgen deficiency [9,10,25]. Body compositional changes, however, are known to occur with aging itself, which may or may not be related to age-related declines in serum testosterone concentrations. Longitudinal studies using hydrodensitometry have shown that fat mass decreases, and lean mass increases during childhood and puberty (when adjusted for stature) [45], followed by an increase in fat and a decrease in lean mass during adulthood [46–49] and very old age [50]. These and other large longitudinal [51,52] studies of at least 100 men are summarized in Table 2, and they collectively show a loss of 0.1 to 0.2 kg/y of lean mass and an increase of 0.1 to 0.6 kg/y of fat mass. Because total weight increases up to the age of 60 and then declines in more than 60% of men, the accumulation of fat mass must occur predominately during midlife [53–55]. The midlife increase in fat mass, which is predominantly abdominal/central, is associated with the metabolic syndrome and is a critical predictor of all-cause mortality [56–58]. How these age-specific body compositional changes relate to changes in serum testosterone, or to changes in integrative gonadotropin axis signaling, is undefined. Hence, although these body compositional changes commonly are considered part of the

Table 2
Age-related changes in body composition

First author, year [Ref.]	N	Baseline age range (y)	Follow-up (y)	Method	Approximate Δ fat (kg/y) mean \pm SEM	Approximate Δ muscle (kg/y) mean \pm SEM
Siervogel, 1998 [46]	202	\approx 35 (18–65)	\approx 10	Hydrodensitometry	\uparrow 0.4 \pm 0.1	\leftrightarrow
Guo, 1999 [47]	102	44 (40–58)	9 (1–20)	Hydrodensitometry	\uparrow 0.4 \pm 0.06	\leftrightarrow
Keys, 1973 [48]	58	22 (18–26)	19	Hydrodensitometry	\uparrow 0.6 \pm ?	\downarrow 0.1 \pm ?
Hughes, 2002 [50]	53	61 (46–80)	9 (5–12)	Hydrodensitometry	\uparrow 0.1 \pm 0.04	\downarrow 0.1 \pm 0.03
Chien, 1975 [49]	27	32 (21–44)	12	Hydrodensitometry	\uparrow 0.6 \pm 0.02	\leftrightarrow
Flynn, 1989 [52]	564	\approx 50 (28–60)	< 18	Total body potassium	\leftrightarrow	\leftrightarrow
Jackson, 1995 [51]	153	46 (25–70)	4	Skinfold thickness	\leftrightarrow	\downarrow 0.1 \pm 0.03

clinical definition of relative androgen deficiency, their diagnostic utility remains unclear.

Similarly, other important somatic features such as muscular strength are known to decline with age. Studies of at least 100 subjects examining the effect of age on upper limb [55,59–62] and lower limb [63,64] strength are summarized in Tables 3 and 4. These show that maximal dynamic force production declines with age in the upper and lower limbs. Furthermore, increasing age seems to be associated with an even greater reduction in percentage strength. Although there are no large series examining the longitudinal decline in lower limb strength (Table 4), smaller longitudinal [65–68] and population-based cross-sectional studies [69] confirm a similar 1% to 3% decrease in strength per year.

All of these somatic features decline with age, irrespective of gender. They often are used in the clinical definition of relative androgen deficiency, but they are unlikely to be useful as currently used. Markers of physical performance such as gait speed [70,71], manual performance [72], ability to stand up from a chair [71] and balance [71] decline with age in longitudinal studies and have been shown in longitudinal [73–78] and cross-sectional [79–81] studies to predict a range of important outcomes (Table 5). These declines also are not universal [71], suggesting the possibility that selective preventative strategies are feasible. Thus these physical performance characteristics may be of paramount importance in selecting subpopulations of older men who comprise the at-risk population likely to become disabled and therefore most likely to benefit from androgen therapy. Such verification

Table 3
Age-related changes in upper limb muscle strength

First author, year [Ref.]	N	Baseline age range (y)	Follow-up (y)	Population	Method	Strength (% decline/y)
Rantanen, 1998 [55]	3741	≈ 55 (45–68)	27	Representative	Handgrip	1 ± 0.01
Metter, 1997 [60]	837	≈ 35 (18–65)	10 (9–57)	Volunteer	Isokinetic	1 ± 0.2
Clement, 1974 [62]	369	≈ 60 (16–90)	10 (5–15)	Representative	Handgrip	1.2
Bassey, 1993 [61]	240	72 (64–94)	4	Representative	Handgrip	3 ± 0.3
Clement, 1974 [62]	1139	≈ 60 (16–90)	0	Representative	Handgrip	0.8
Metter, 1997 [60]	993	≈ 35 (18–65)	0	Volunteer	Isokinetic	< 1
Bassey, 1993 [61]	354	74 (> 60)	0	Representative	Handgrip	2
Baumgartner, 1999 [59]	121	77 (65–97)	0	Volunteer	Handgrip	< 1

Table 4
Age-related changes in lower limb muscle strength

First author, year [Ref.]	N	Baseline age range (y)	Follow-up (y)	Population	Method	Strength (% decline/y)
Lindle, 1997 [63]	346	≈ 55 (20–93)	0	Volunteer	Isometric	< 1
Fisher, 1990 [97]	116	≈ 40 (20–79)	0	Volunteer	Isometric	< 1
Larson, 1979 [64]	114	≈ 40 (11–70)	0	Volunteer	Isometric	< 1

will require large randomized placebo-controlled studies examining baseline somatic characteristics in careful prospectively planned analyses to identify an androgen responsive subgroup, or specific and strict entry criteria based on physical performance.

Psychologic and cognitive symptoms

Depressed mood, irritability, inability to concentrate, and other mild and subtle psychologic and cognitive disturbances are reported universally in men with organic androgen deficiency. Such features also are used to determine relative androgen deficiency in older men [9,10,25]. Interpretation is convoluted, because depression increases with age, even in very old age [82]. Secondly, either dysthymia or major depression may suppress serum testosterone concentrations modestly in older men [83]. A further complication arises from varying androgen receptor polymorphisms, because systemic testosterone predicts depression, but only in the subgroup of men with shorter CAG repeats [84]. Although these data suggest the importance of testosterone in depression, randomized trials examining the effect of testosterone therapy on mood in depressed men with lower serum testosterone concentrations

Table 5
Poor physical performance leads to disability

First author, year [Ref.]	N	Age (y)	Follow-up (y)	Physical function	Predicts
Dargent-Molina, 1996 [75]	7575	> 75	2	Gait, dynamic balance	Hip fracture
Penninx, 2000 [73]	3381	> 70	4	Gain, balance, chair rise	Hospitalization
Guralnik, 1995 [76]	1122	> 70	4	Gait, balance, chair rise	Disability
Tinetti, 1988 [78]	336	> 70	1	Gait, balance, chair rise	Falls
Vellas, 1997 [74]	316	> 60	3	Static balance	Injurious falls
Reuben, 1992 [77]	149	> 70	2	Gait, physical performance	Mortality and nursing home placement
Guralnik, 1994 [81]	5174	> 70	0	Gait, balance, chair rise	Mortality
Ferrucci, 2000 [79]	3381	> 70	0	Gait, balance, chair rise	Hip fracture
Judge, 1996 [80]	2190	> 65	0	Gait, balance, chair rise	Disability

have shown no benefit [85]. This indicates that selecting responsiveness solely on systemic testosterone exposure may not correctly identify the androgen-responsive population with relative androgen deficiency.

The use of psychologic outcomes for assessing relative androgen deficiency is also problematic, because accurate assessments are made difficult by the low motivation of severe depression and the disorganized thought of anxiety-related illness, either of which may be present to some degree in older men. When the underlying psychiatric disorder improves, self-perception is likely to change independent of objective changes. For these reasons, the use of psychologic outcomes in the definition of relative androgen deficiency is especially uncertain.

Similarly, in older men, lower testosterone concentrations are associated with poorer cognitive function [86,87] and predict faster decline in visual memory [87]. There is growing evidence that androgens, possibly after local aromatization, are important for spatial cognition and some aspects of memory in older men. Whether differences are caused by subtle differences in testing procedures, duration and dose of administration, baseline androgen status, or baseline cognitive ability is unknown. The detrimental effects of androgen therapy on spatial cognition only have been detected at higher doses [88,89], whereas beneficial [90–92] or no [93–95], effects only have been shown at lower doses. This observation is coherent with the putative U-shaped relationship between serum testosterone and spatial cognitive abilities reported in cross-sectional studies in men [96]. These uncertainties and the relative difficulty in assessing these cognitive functions in clinical practice makes it seem improbable that any of these features can be used alone to adequately define relative androgen deficiency. Although these psychologic and cognitive symptoms are unlikely to be useful diagnostically, their utility in monitoring treatment has not been studied adequately.

Summary

Serum total, free, and non-SHBG-bound testosterone concentrations decline progressively with age. In many older men, the resulting testosterone levels fall below the normal reference range established in healthy young men, therefore demonstrating statistically definable relative testosterone deficiency. Many older men have symptoms indicative of organic testosterone deficiency. The classical clinical features of organic testosterone deficiency, however, have limited specificity in the older man because of multiple coexisting etiologies. Individual symptoms are androgen responsive; none of the sexual, somatic, or psychologic features commonly used are sensitive or specific for androgen deficiency. For example, even questionnaires developed to screen on the basis of low serum testosterone concentrations have poor sensitivity (ranging from 75% to 90%) and specificity (ranging from 50% to 60%) for this outcome [9,10]. Furthermore, whether this inaccuracy can be improved by combining multiple symptoms has not been studied adequately.

Future research exploring the putative clinical syndrome of relative androgen deficiency in older men should be focused primarily on randomized clinical trials that unequivocally demonstrate health outcome benefits with androgen therapy. This will help establish the parameters that will identify those who are most likely to benefit from androgen therapy. At this stage, the clinician will have to be vigilant in identifying cases, because many of the sexual, somatic, and psychologic indicators are nonspecific. Future research also should focus on identifying those at risk of disability (particularly by examining specific somatic features) and elucidating simple clinical biomarkers of testosterone response (possibly in the psychologic and cognitive domains). To this end, monitoring a single symptom or a limited collection of related symptoms, which may differ from person to person, may be more useful than a wide-ranging questionnaire with multiple endpoints, some of which are likely to be irrelevant to any given person. Until more answers become available, clinicians are left with best practice guidelines and recommendations for future research [5,6].

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