**Table 1-5** Major depressive episode – The Mini-International Neuropsychiatric Interview (M.I.N.I), Japanese version 5.0.0 (2003), Modified

| | | | |
|---|---|---|---|
| A1 | Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks? | No | Yes |
| A2 | In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time? | No | Yes |
| | Is A1 or A2 coded Yes? | No | Yes |
| A3 | Over the past two weeks, when you feel depressed or uninterested: | | |
| a | Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e. by ± 5% of body weight or ±3.5 kg for a 70 kg person in a month)? If yes to either appetite change or body weight change, code Yes. | No | Yes |
| b | Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)? | No | Yes |
| c | Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day? | No | Yes |
| d | Did you feel tired or without energy almost every day? | No | Yes |
| e | Did you feel worthless or guilty almost every day? | No | Yes |
| f | Did you have difficulty concentrating or making decisions almost every day? | No | Yes |
| g | Did you repeatedly consider hurting yourself, feel suicidal or wish that you were dead? | No | Yes |
| | Are 5 or more answers (A1-A3) coded Yes? | **No** | **Yes** |
| | | | **Major depressive episode, current** |
| | If a patient has a current major depressive episode, continue to A4. Otherwise, continue to **Table 1-6**, B1. | | |
| A4 | | | |
| a | During your lifetime, did you have other episodes of two weeks or more when you felt depressed, or uninterested in most things, and had most of the problems we just talked about? | No | Yes |
| b | In between two episodes of depression, did you ever have an interval of at least two months without any depression and any loss of interest? | **No** | **Yes** |
| | | | **Major depressive episode, recurrent** |

**Diagnostic method**

If either A1 or A2 are coded Yes and five or more answers of the nine questions from A1 to A3 are coded yes = major depressive disorder → **Major depressive disorders were handled by the departments of neuropsychiatry or psychosomatic medicine.**

If both A1 and A2 are coded No and less than 5 of the answers of the nine questions from A1 to A3 are coded Yes → **Move to 'Dysthymic disorders'** (Table 1-6).

**7** In interventional research on coronary artery disease using testosterone, it was reported that electrocardiographic ST segment depression due to exercise was improved by ART in patients with coronary artery disease.[36–38] In short-term research, administration at the time of attacks was ineffective and had no effect on the number of attacks. It was also reported that the number of attacks could be decreased and the tolerated level of exercise increased. However, it is not clear if ART is connected with the prevention of the onset of coronary artery disease.

## 2 Indications for ART (Table 1-8)

**1** ART is indicated for men over the age of 40 with signs and symptoms of LOH when there is a drop in the free testosterone blood level.

**2** ART is first-line treatment when the free testosterone blood level is less than the 8.5 pg/mL, the mean–2SD of men in their twenties.[11]

**3** ART should be considered for men with a free testosterone level of less than 11.8 pg/mL, 70% of the mean value (16.8 pg/mL) of men in their twenties (YAM value), i.e. greater than 8.5 and less than 11.8 pg/mL, which tends to be deficient but is within the normal range. Based on the severity of signs and symptoms, ART is a treatment option after the risks and usefulness of ART have been explained to the patient.

**4** ART is not performed when the free testosterone blood level is 11.8 pg/mL or higher, and the following treatment is considered based on the symptoms. When sexual function symptoms are severe, a PDE5 inhibitor is administered. When psychological symptoms are severe, a neuropsychiatrist or psychosomatic physician is consulted and antidepressants or antianxiety agents are administered. When physical symptoms are severe, if osteoporosis is suspected, consultations are held with a specialist and drug therapy is considered, and for reductions in muscle strength, guidance is given on lifestyle improvements.

## 3 ART exclusion criteria

ART is not performed in patients with the diseases or conditions shown in Table 1-9.

## 4 ART protocols

### 1) Protocols

The following three ART protocols are recommended.

**1** Testosterone enanthate is administered intramuscularly at 125 mg each time every two or three weeks or 250 mg each time every three to four weeks.

**Table 1-6** Dysthymic disorders – The Mini-International Neuropsychiatric Interview (M.I.N.I), Japanese version 5.0.0 (2003), Modified

| | | | | |
|---|---|---|---|---|
| If the patient's symptoms currently meet criteria for a major depressive episode, do not explore this module. | | | | |
| B1 | | Have you felt sad, low or depressed most of the time for the last two years? | No | Yes |
| B2 | | Was this period interrupted by your feeling OK for two months or more? | No | Yes |
| B3 | | During this period of feeling depressed most of the time: | No | Yes |
| | a | Did your appetite change significantly? | No | Yes |
| | b | Did you have trouble sleeping or sleep excessively? | No | Yes |
| | c | Did you feel tired or without energy? | No | Yes |
| | d | Did you lose your self-confidence? | No | Yes |
| | e | Did you have trouble concentrating or making decisions? | No | Yes |
| | f | Did you feel hopeless? | No | Yes |
| | | Are two or more B3 answers coded yes? | No | Yes |
| B4 | | Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially or in some other important way? | No | Yes |
| | | Is B4 coded Yes? | **No** | **Yes** |
| | | | | **Dysthymic disorder current** |

Diagnostic method
Dysthymic disorder (not major depressive disorder, but pathological depressed state continues for a long time)
→ **Handled by the departments of neuropsychiatry or psychosomatic medicine.**
If B1 is coded No, B2 is coded Yes, or less than two of the answers of the six questions from B3 is coded Yes = **Not dysthymic disorder**
If B1 is coded Yes, B2 is coded No, two or more of the answers of the six questions from B3 are coded Yes, and B4 Yes = **Diagnosed as dysthymic disorder**

**Table 1-7** Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence

| | | | |
|---|---|---|---|
| These questions concern daily activities. Reply to the following questions by encircling either Yes or No. Please answer all questions. | | | |
| (1) | Can you go out alone using a bus or train? . . . . . | 1. Yes | 2. No |
| (2) | Can you purchase your own daily necessities? . . . . . | 1. Yes | 2. No |
| (3) | Do you prepare your own food? . . . . . | 1. Yes | 2. No |
| (4) | Can you pay your bills? . . . . . | 1. Yes | 2. No |
| (5) | Can you handle your bank or post office account by yourself? . . . . . | 1. Yes | 2. No |
| (6) | Do you prepare documents concerning your pension, etc.? . . . . . | 1. Yes | 2. No |
| (7) | Do you read the newspaper? . . . . . | 1. Yes | 2. No |
| (8) | Do you read books or magazines? . . . . . | 1. Yes | 2. No |
| (9) | Are you interested in articles or programs about health? . . . . . | 1. Yes | 2. No |
| (10) | Do you visit the homes of friends? . . . . . | 1. Yes | 2. No |
| (11) | Do you discuss matters with your family or friends? . . . . . | 1. Yes | 2. No |
| (12) | Can you visit people who are sick? . . . . . | 1. Yes | 2. No |
| (13) | Do you try to talk to young people? . . . . . | 1. Yes | 2. No |

Since the maximum testosterone blood levels are reached in about four to seven days after administration, caution is required because of the possibility that the serum testosterone levels will exceed normal values and reach a non-physiological level when the single dose is high. It is recommended that blood be collected once about four to seven days after administration and the concentration of free testosterone in the blood be measured.

**2** Human chorionic gonadotropin (hCG) is administered intramuscularly at 3000–5000 units each time once or twice a week or every two weeks.

The hCG test is performed on patients with normal LH blood levels and if the response of testosterone in the blood is good, hCG is administered.[39] The advantage is that changes in blood testosterone are relatively small when compared with those of testosterone enanthate, and the disadvantage is that many administrations are required.

**3** Testosterone ointment is applied at a dose of 3 g each time once or twice a day on the skin of the scrotum (equivalent to 3 mg of testosterone each time). Administration is easy and stable testosterone concentrations in the blood are obtained.[40]

### 2) Treatment period

With all methods, evaluation is performed every three months after the start of treatment. If effects are observed, treatment is continued with caution concerning adverse reactions.

**Table 1-8** Indications of androgen replacement therapy (ART)

| | Men over 40 years of age with the Late-onset Hypogonadism signs and symptoms and free testosterone blood levels as follows. |
|---|---|
| Less than 8.5 pg/mL | ART is first line therapy. |
| 8.5 pg/mL to 11.8 pg/mL | Based on severity of signs and symptoms, ART is one treatment option after the risks and usefulness have been explained to the patient. |
| 11.8 pg/mL and higher | ART is not performed and the following treatment is considered based on the symptoms.<br>• Sexual function symptoms: phosphodiesterase type 5 (PDE5) inhibitor<br>• Mental and psychological symptoms: consultation with a neuropsychiatrist or psychosomatic physician and administration of antidepressants or antianxiety drugs<br>• Physical symptoms: consultation with a specialist on osteoporosis, drug therapy and guidance on life style improvements for reduced muscle strength |

**Table 1-9** Androgen replacement therapy (ART) exclusion criteria

| | |
|---|---|
| • Prostate cancer | • Polycythemia |
| • Pretreatment PSA values of not less than 2.0 ng/mL | • Severe hepatic dysfunction |
| Treatment should be performed with caution when the PSA value is not less than 2.0 and less than 4.0 ng/mL | • Severe renal failure<br>• Congestive heart failure |
| • Moderate to severe benign prostatic hyperplasia | • Severe hypertension |
| • Breast cancer | • Sleep apnea |

PSA, prostate specific antigen.

### 3) Contraindicated concomitant medication

Contraindicated concomitant medication for male testosterone enanthate are warfarin potassium and other anticoagulants. Since the action of anticoagulants is intensified by concomitant administration, caution is required including reducing the dose of the anticoagulants.

## [4] Adverse reactions of androgen replacement therapy (ART) and their monitoring

### 1 ART adverse reactions and complications

Androgens are steroid hormones that act on many organs and tissues. Risks that should be considered when performing ART include cardiovascular diseases, lipid metabolism disorders, polycythemia, fluid retention, prostatic hyperplasia, prostate cancer, hepatotoxicity, sleep apnea, gynecomastia, acne, testicular atrophy, infertility, and changes in behavior or mood.[3,41]

### 1) Adverse reactions

**1** Cardiovascular diseases

It has been reported that the prevalence of coronary artery disease is high in patients with hypogonadism.[42,43] However, no effects of long-term ART on the cardiovascular system have been confirmed and cardiovascular testing is required depending on clinical symptoms.

**2** Lipid metabolism

No adverse effects on lipid metabolism have been found with ART when blood testosterone levels do not exceed the physiological range during treatment.[44,45] Decreases in blood levels of HDL cholesterol have been observed at high doses.[44]

**3** Polycythemia

Polycythemia that requires suspension of thrombectomy or cessation of ART is observed in 24% of patients with hypogonadism treated with ART.[46] During treatment, it is necessary to monitor polycythemia by periodic blood tests. The criteria for polycythemia are red blood cell (RBC) counts $6 \times 10^6/\mu L$ or more, hemoglobin of 18 g/dL or more and hematocrit of 53%. In such conditions, adjustment of ART intervals and consultations by a hematologist are needed.

**4** Hepatotoxicity

Hepatic dysfunction has been found in about one third of patients administered testosterone orally,[47] but hepatic dysfunction due to oral administration of testosterone undecanoate or intramuscular administration of testosterone enanthate is rare.[48]

**5** Sleep apnea

Since ART can exacerbate sleep apnea,[49,50] ART is contraindicated for patients with sleep apnea.

**6** Other adverse reactions

Acne, increased body hair and flushing have been observed but they are not significant adverse reactions.[51]

### 2) Monitoring of ART adverse reactions (Table 1-10)

At baseline, physical examination and laboratory tests, an evaluation of voiding conditions using IPSS and history of sleep apnea should be ascertained. In hematology, hemoglobin, hematocrit and RBC count are especially important. In blood chemistry, TC, TG, HDL-C, LDL-C, GOT, GPT, ALP, γ-GTP, FBS and $HbA_{1c}$ must be tested. Routine urinalysis including urinary sugar must be checked periodically. Blood tests should be checked two to four weeks, three months, six months and twelve months after the initiation of the treatment and once a year thereafter. Treatment must be discontinued or the dose is adjusted as required based on the test values. Voiding conditions and sleep apnea should be monitored and if abnormalities are found, treatment is discontinued or doses should be reduced, and then referred to specialists as required. Periodic cardiovascular examinations are not necessary, but when abnormalities are discovered by tests performed, ART should be discontinued and an evaluation by a specialist is needed.

### 2 ART and prostate disease

Caution is required in relation to prostate disease, which is a risk for ART. ART is absolutely contraindicated in cases of prostate cancer and relatively contraindicated for prostatic hyperplasia. ART and prostate disease are discussed from three standpoints: prostatic hyperplasia, prostate cancer and the serum prostate specific antigen (PSA) value.

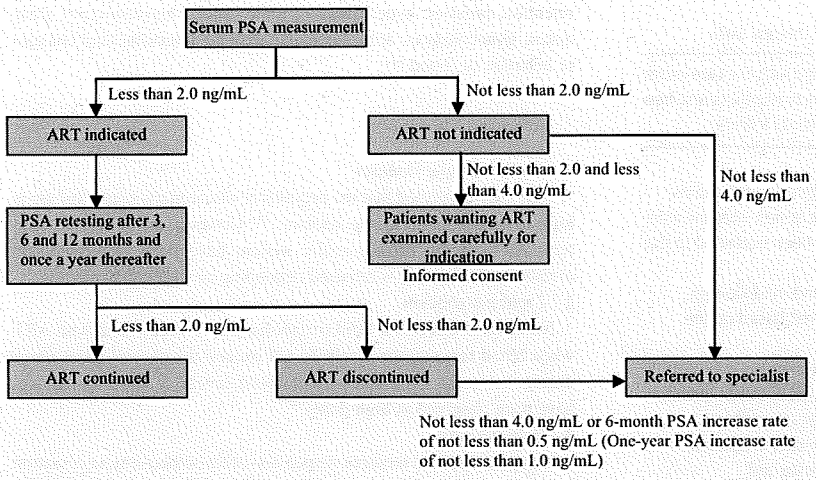


**Fig. 4** Evaluation of PSA values at start of and during ART.

**Table 1-10** Monitoring to avoid androgen replacement therapy (ART) adverse reactions

| Course | Monitored items |
|---|---|
| Before treatment | • General examination and laboratory tests<br>• Questionnaire on voiding conditions<br>• Checking for sleep apnea<br>• Serum PSA |
| After treatment | • Optimal dose set after 1–2 months based on clinical symptoms<br>• Blood tests (after 2–4 weeks, 3 months, 6 months and 12 months and once a year thereafter)<br>• Monitoring of voiding conditions and sleep apnea<br>• Serum PSA |

PSA, prostate specific antigen.

### 1) Effect of ART on prostatic hyperplasia and dysuria

In comparison with a placebo group, the ART group showed no worsening of voiding symptoms or complications due to prostatic hyperplasia.[24,30,52–57] In short-term ART (maximum of 36 months) in elderly men, no clear changes in prostate size, urinary flow rate or IPSS were reported.[58] However, the prostate is known to be androgen dependent[59] and prostate weight usually decreases with antiandrogen therapy. It is necessary to consider enlargement of the prostate due to ART.

### 2) Relation between ART and prostate cancer

There is little evidence that ART causes prostate cancer but there are case reports suggesting the progression from latent cancer to clinical cancer.[60,61] In prospective studies,[27,28,44,57,62] prostate cancer appeared in five out of 461 patients (1-%) given ART for 6–36 months, but this was the same as the general prevalence. However, the effects of long-term treatment for more than 36 months are unclear. Therefore, the serum PSA value must be carefully monitored as described below.

### 3) ART and Serum PSA values

Appropriate Serum PSA monitoring is important for early discovery of prostate cancer. The PSA criteria for ART are shown in Figure 4.

1 PSA of less than 2.0 ng/mL is recommended as the standard value for indicating ART. There is no evidence for this standard value. One report concluded that a standard value of 4.0 ng/mL is generally appropriate[41] while another report concluded that ART is not performed at 3.0 ng/mL. In addition, there are reports that latent cancer[63,64] and highly atypical cancer[64,65] are likely to occur in the low testosterone group. In this Manual, the PSA standard value was set at a low value.
2 ART should be considered after a careful investigation when PSA is greater than 2.0 and less than 4.0 ng/mL. In Western countries, ART is sometimes performed after prostate biopsies.[54]
3 When PSA is greater than 4.0 ng/mL or when other findings of suspected prostate cancer are obtained, a specialist should be consulted.
4 ART should be discontinued and a specialist consulted when PSA increases by greater than 0.5 ng/mL at six months or greater than 1.0 ng/mL at one year after start of ART.

## [5] Assessment after treatment

Treatment of LOH is usually continued for a long time. When ART is performed, blood levels of testosterone basically increase in all patients. It is necessary to assess the signs and symptoms of LOH associated with improvements in blood testosterone levels as treatment effects. Since evidence has still not been established for the therapeutic effects on LOH Syndrome in particular, it is necessary to accumulate evidence by global evaluations. This is the objective of this Manual.

The therapeutic effects are usually evaluated at least every three-months at one year after the start of treatment and the intention of the patient, including continuing or discontinuing treatment, is confirmed. When treatment is performed for more than one year, it is important to observe variations in the symptoms periodically. In the official recommendation by ISSAM in 2002, it states 'Observation of the course during ART is the responsibility of both the physician and the patient. The necessity of periodic evaluations of patients by physicians must be stressed and the patients must agree to follow these requirements.' Thus, the importance of periodic evaluations by both physicians and patients is emphasized.[3] This recommendation includes the statement that 'Hormone replacement therapy is normally performed for life and observation of the course is also a lifetime duty.' However, time is required before this point is clearly understood in Japan. At present, it

cannot be stated that it is necessary to continue for the rest of the patient's life once ART is started, and therefore it is necessary for both the physician and patient to have a common understanding of the treatment period. When adverse reactions appear, there are cases when treatment should be discontinued even though the treatment was found to be effective.[4–7]

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連載 泌尿器科における各種ガイドラインの読み方
第8回
泌尿器外科 2010年 23(1), 51～54

# 加齢男性性腺機能低下症候群（LOH症候群）診療の手引き

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## 加齢男性性腺機能低下症候群（LOH症候群）診療の手引き」作成の経緯

加齢男性性腺機能低下症候群（late-onset hypogonadism：以下，LOH症候群）は男性ホルモンの部分欠乏に因る症状，および徴候からなる症候群であるが，以前は加齢に伴う生理現象とされ，診療対象ではなかった。しかし，高齢化社会の到来により，高齢者のQOLをいかに維持するかが，21世紀医療の大きなテーマとなってきた。ところが，女性に対するホルモン補充が国際的に広く普及しているのに対し，高齢男性に対する医療はEDに対するphosphodiesterase type 5阻害薬の普及以外，あまり医療の対象となってこなかった。このような高齢男性への医療対策の遅れが直接原因ではないものの，近年男女間の平均寿命の差が大きく開き，本邦では約7歳男性寿命の方が短い。この事実がWHOを後押しし，1998年にGeneve Manifestが発せられるに至り，"Healthy aging for men"がようやく国際的な流れになってきた。そして"The aging male research on gender specific issues in male health"を目的に1998年に国際Aging Male学会（以下，ISSAM）が設立され，日本でも2001年に日本Aging Male研究会が設立された。ところが当時，有名人の男性更年期障害体験談がマスコミで大きく取り上げられ，LOH症候群診療を始めたばかりの診療現場に男性更年期障害を主訴とする患者が多く受診した。男性更年期障害はLOH症候群の一症状であるが，うつ病と紛らわしく診療現場で混乱も生じた。国際的には2005年のISSAMからLOH診療に対するrecommendation[1]が発表されていたが，テストステロン値ひとつとっても，測定しているテストステロンの種類や基準値が海外と異なるなど不都合が少なくなかったため，本邦独自のLOH症候群診療ガイドライン作成のワーキンググループが組織された。そのワーキンググループの審議および日本Aging male研究会（2006年から日本Men's Health医学会に名称変更）学術集会での討議の中で，ガイドラインという名称にするにはエビデンスレベルが低いとの指摘があり，最終的に「加齢男性性腺機能低下症候群（LOH症候群）診療の手引き」が2007年1月に発刊されるに至った。

## 定義およびガイドラインの対象

まず，男性更年期障害とLOH症候群の位置付けを明らかにした（**図1**）。すなわち，男性更年期障害は主に更年期に発症する多彩な身体，精神症状を伴う疾患であり，その原因としてアンドロゲンの低下のみならず，ホルモン以外の精神的，身体的因子が関与している場合が少なくない。したがって，アンドロゲン低下を伴わない場合，アンドロゲン補充の適応とならない。一方，LOH症候群は加齢に伴うアンドロゲン低下が原因となっている。この中には男性更年期障害の一部も含まれるが，自覚症状を伴わないアンドロゲン低下に起因する様々な徴候が含まれる（**図2**）。したがって，LOH症候群の治療の基本はアンドロゲン補充である。

以上のような両疾患の位置付けを明らかにした上で，今回の診療ガイドラインの対象としてLOH症候群を採用した。

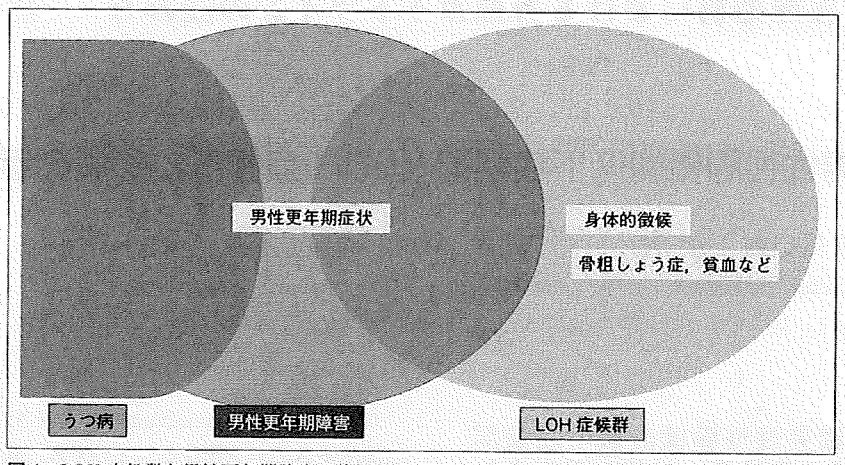


図1 LOH症候群と男性更年期障害の位置付け

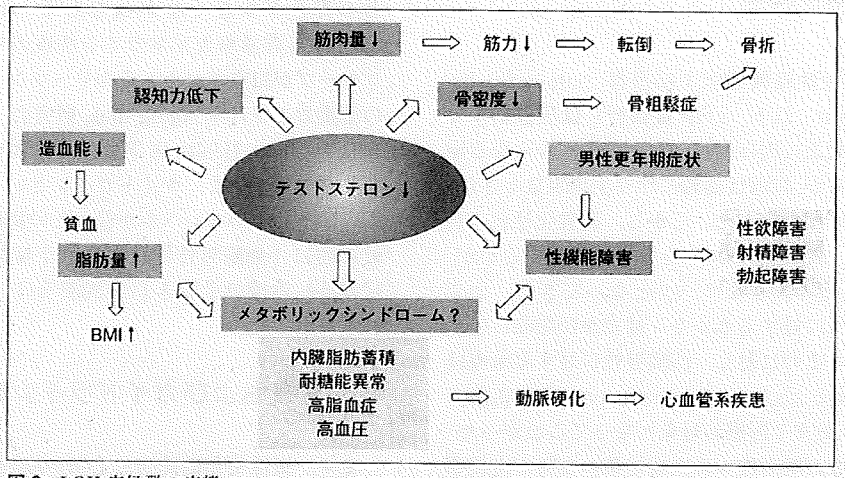


図2 LOH症候群の病態

## LOH症候群の診断とホルモン補充療法の適応

### 1. ホルモン学的検査の実際

主な男性ホルモンは精巣で産生されるテストステロンである。血中における活性型テストステロンは遊離型（フリー）テストステロンであり，総テストステロンの1～2%に過ぎない。総テストステロンは，sex hormone-binding globulin (SHBG) とテストステロンの結合型，アルブミンとテストステロンの結合型，および遊離型テストステロンの3分画よりなる。アルブミンに結合するテストステロンは容易にアルブミンから解離するため，遊離型テストステロンとアルブミン結合型テストステロンを合わせて生物活性をもつバイオアベイラブル（bioavailable）テストステロン（BAT）と呼ばれている。

ゴナドトロピン測定は，原発性性腺機能低下症と2次性性腺機能低下症の鑑別に有用である。したがって男性ホルモンが低下している場合には下垂体ホルモンとして黄体化ホルモン（LH），卵胞刺激ホルモン（FSH）の測定が必要である。

副腎アンドロゲンであるdehydroepiandrosterone（DHEA）は加齢により漸減するので，老化指標の1つであるとともにLOH症状および徴候を惹起する可能性がある。また，血中コルチゾールは生涯を通じて変動を認めないが，ストレスで変動することが知られているので，LOH症候群と一過性ストレスとの鑑別に有用である。

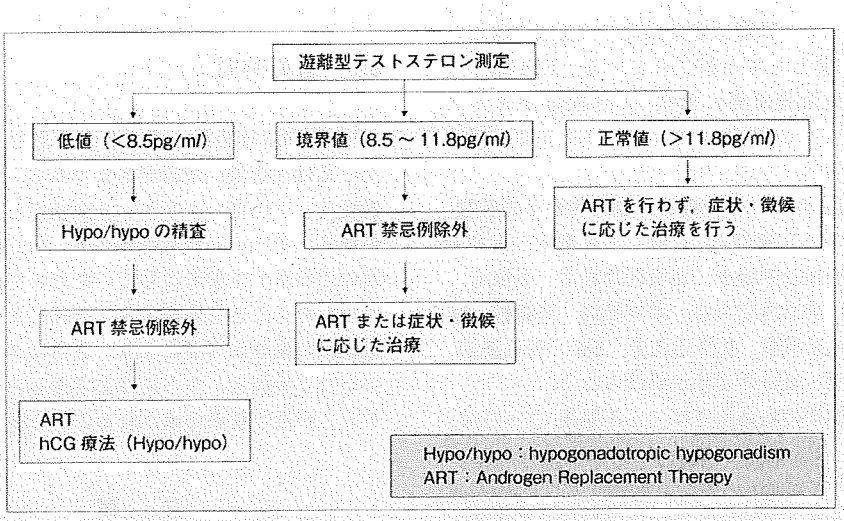


図3　LOH 症候群の診断・治療のアルゴリズム

**2. ホルモン補充療法の適応基準値**

ISSAM の Recommendation では LOH の基準値は総テストステロン値により定めている。しかし，本邦の健常男性の検討から[2] 総テストステロンは加齢による減少が軽度であり，それに対し遊離型テストステロン値は有意に加齢とともに減少すること，および健康保険の関係で総テストステロンと遊離型テストステロンを同時に測定できないことなどから，「LOH 症候群診療の手引き」では遊離型テストステロンを LOH 診断検査とすることを推奨している。

遊離型テストステロン値は一律に平均値で示すことは無理がある。そこで LOH 症候群の診断基準値として 20 歳代の mean-2SD である 8.5pg/ml を正常下限値とした。さらに 8.5pg/ml 以上であっても 20 歳代の平均値（Young Adult Mean, YAM）の 70%値である 11.8pg/ml 未満までの症例は男性ホルモン低下傾向群（LOH のボーダーライン症例）とすることが LOH 症候群診断のアルゴリズムとして提案されている（図3）。

## 治療の実際

**1. 男性ホルモン補充療法（以下，ART）の適応**

前項で述べた基準に基づき，ART の適応が以下のごとく決められている。

まず，血中遊離型テストステロンが 8.5pg/ml 未満の場合，ART を第一に行う。

遊離型テストステロンが 11.8pg/ml 未満で，かつ 8.5pg/ml 以上である低下傾向群では，症状および徴候の程度に応じ，患者に ART のリスクと有用性を説明した上で ART を治療の一選択肢とする。

遊離型テストステロン値が 11.8pg/ml 以上の場合 ART は行わず，症状の内容により以下の治療を考慮する。性機能症状が強い場合は PDF5 阻害薬を投与する。心理症状が強い場合は精神神経科医・心療内科医と相談し，抗うつ薬，抗不安薬を投与する。身体症状が強い場合，骨粗しょう症が疑われる場合は専門医と相談し薬物療法を検討し，筋力低下に対しては生活習慣の改善などを指導する。

**2. 男性ホルモン補充療法の除外基準**

前立腺癌患者や睡眠時無呼吸発作を有する場合は ART を行わない。PSA 値では 2ng/ml 以上の場合は男性ホルモン補充療法を相対的禁忌としている。その他，重篤な内臓疾患を有する患者は除外されている。

**3. アンドロゲン補充療法のプロトコール**

実際の ART の方法として我が国では以下の 3 つが推奨されている。

まず，エナント酸テストステロン筋注であり，1 回 125mg を 2～3 週毎または 1 回 250mg を 3～4 週毎に投与する。

血中 LH 正常例に対しては hCG 負荷試験を行い，血中テストステロンの反応性が良好であれば hCG を投与する。hCG1 回 3,000～5,000 単位を週 1～2 回または 2 週間毎の筋注が推奨される。

男性ホルモン軟膏は健康保険では使用できないが，OTC薬として市販されている。1回3gを1日1～2回陰嚢皮膚に塗布（1回3mgテストステロン相当）で安定した血中テストステロン濃度が得られる[7]。

**4. 男性ホルモン補充療法の副作用とその監視**

男性ホルモン補充療法に際して考慮すべきリスクとして心血管系疾患，脂質代謝異常，多血症，体液貯留，前立腺肥大症，前立腺癌，肝毒性，睡眠時無呼吸症候群，女性化乳房，ざ瘡，精巣萎縮，不妊，行動・気分の変化が挙げられる。

治療開始後の血液検査は2～4週後，3ヵ月後，6ヵ月後，12ヵ月後，以後は1年毎に行い，検査値に基づいて治療の中止または適宜投与量の増減を行う。また，適宜専門医に患者の治療を依頼する。

## おわりに

LOH診療は始まったばかりであり，診療にあたっては注意深い配慮が必要である。また，今後推奨ランクの高いエビデンスを創出していく必要がある。そういった意味からも，「LOH症候群診療の手引き」を参考にしていただいて診療を行っていただくことを希望する。それにより，今後診療結果の検証が可能になり，さらにグレードアップした「手引き」さらには文字通りの「ガイドライン」が近い将来作成されることを願っている。

### 文　献


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男性ホルモンの臨床

# ホルモン補充療法の実際

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**プライマリ・ケアにおけるポイント**

加齢男性性腺機能低下症候群（LOH症候群）は，加齢に伴う相対的な男性ホルモンの低下により惹起するさまざまな身体の異常であるため，診断として遊離テストステロンの測定が必須である．また，男性ホルモン補充に当たっては，除外基準である前立腺癌や睡眠時無呼吸発作の有無などを調べるのみならず，男性ホルモン補充療法中も副作用の出現がないか，定期的な監視が必要である．LOH症候群診療は，まだ始まったばかりの診療であるため，「LOH症候群―加齢男性性腺機能低下症候群診療の手引き」[1]などを参考にしながら，慎重に診療を行うことが推奨される．

## はじめに

従来，ホルモン補充療法は絶対的な男性ホルモン低下をきたす性腺機能低下症に行われており，原発性に対しては男性ホルモン剤が，二次性に対してはLH-RH，hCGまたは男性ホルモン剤が病態に応じて使用されてきた（図1）．しかし最近は，**加齢に伴う相対的な男性ホルモンの低下もさまざまな身体の異常を惹起することが注目され，診療の対象になってきた．**

本稿ではメンズヘルスの観点から論じるため，後者の加齢男性性腺機能低下症候群（late-onset hypogonadism：LOH症候群）に対するホルモン補充療法について，その背景，適応および治療の実際について述べる．

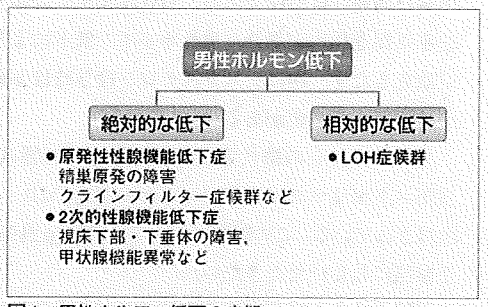


図1 男性ホルモン低下の病態

## I 男性ホルモン低下に伴う症状・徴候および男性ホルモン補充の意義

男性ホルモンは全身のさまざまな臓器を標的とし，多くの重要な生理的働きを担っているため，その低下により，筋，骨，中枢神経系，前立腺，骨髄，性機能などへ影響がある（図2）．

男性ホルモンと筋肉量は正の相関を示すことが知られており，男性ホルモン補充により筋肉量と筋力の増加の報告がある[2]．骨への作用は骨形成を促進し，骨吸収を抑制する作用があると考えられている．テストステロンの骨量維持作用の一部は体内で転換されるエストロゲンの作用を介するが，男性ホルモン低下と骨塩量低下の相関も知られており，男性ホルモン補充による骨塩量増加については多くの報告がある[3]．性機能に関連する作用としては，性欲の維持，射精，勃起作用があ

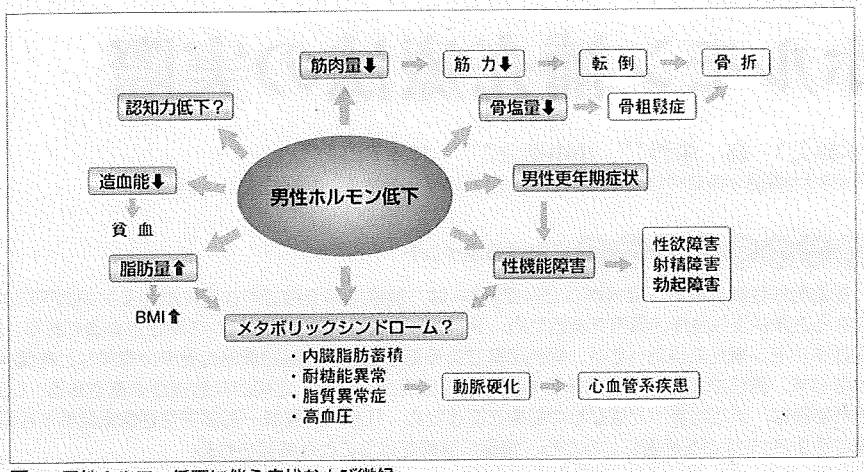


図2 男性ホルモン低下に伴う症状および徴候

り．男性ホルモン補充は男性ホルモン低下を伴う性機能障害には有効である．男性ホルモンと認知力の維持や情動との関連性も示唆されているが，明確な関連性は不明である．男性ホルモンは赤血球産生促進作用があり，男性ホルモン低下により貧血をきたす．逆にテストステロン投与時は多血症に注意する必要がある．

男性ホルモンの糖代謝，脂質代謝への影響は，近年メタボリックシンドロームとの関連において注目されている．この問題については別稿（p.2195）を参照にしていただきたい．

男性ホルモン低下に伴う症状として，当初男性更年期症状が注目されたが，**男性更年期障害は必ずしも男性ホルモン低下を伴うとは限らず，LOH症候群と男性更年期障害とは異なる疾患概念であることに注意する必要がある**（図3）．男性更年期障害については別稿（p.2201）を参照にしていただきたい．

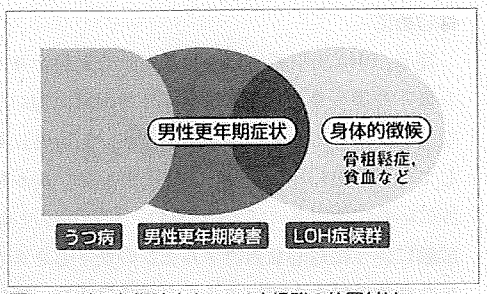


図3 男性更年期障害とLOH症候群の位置付け

## Ⅱ 男性ホルモン低下の診断とホルモン補充療法の適応

LOH症候群は男性ホルモン低下に伴う症候群であるため，ホルモン学的検査が必須である．ホルモン学的検査の中心は血中テストステロンであり，その生化学的な多様性や特性を十分に把握して検査値を分析する必要がある．

### 1 ホルモン学的検査の実際

#### a. ゴナドトロピンとほかの下垂体系ホルモン

ゴナドトロピン測定は，原発性性腺機能低下症と二次性性腺機能低下症の鑑別に有用である．したがって，男性ホルモンが低下している場合には，下垂体ホルモンとして黄体化ホルモン（LH），卵

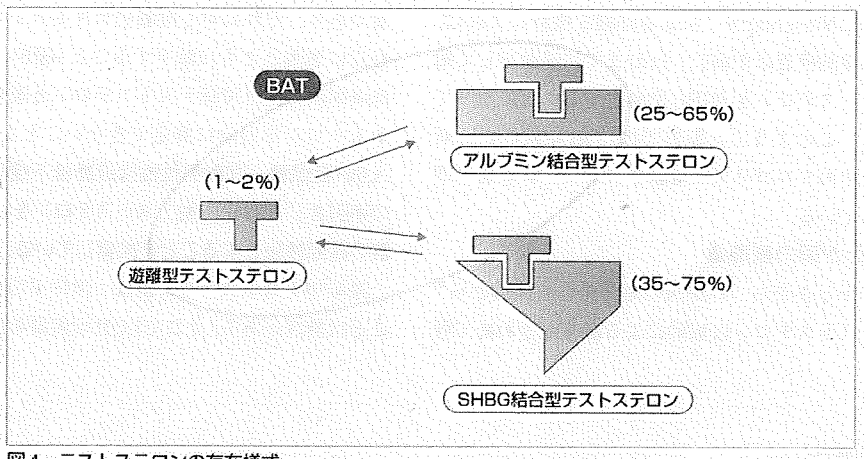


図4　テストステロンの存在様式

胞刺激ホルモン(FSH)の測定が必要である．プロラクチン(PRL)は性機能低下，PRL産生腫瘍などにより高値をきたすことがあるため，測定することが望ましい．

### b．テストステロン

主な男性ホルモンは精巣において産生されるテストステロンである．血中における活性型テストステロンは遊離型(フリー)テストステロンであり，総テストステロンの1～2%に過ぎない．総テストステロンは，①sex hormone-binding globulin (SHBG)とテストステロンの結合型，②アルブミンとテストステロンの結合型，③遊離型テストステロンの3分画よりなる．アルブミンに結合するテストステロンは容易にアルブミンから解離するため，**遊離型テストステロンとアルブミン結合型テストステロンを合わせて，生物活性をもつバイオアベイラブル(bioavailable)テストステロン(BAT)と呼ばれている**(図4)．一方，SHBGはテストステロンと強く結合し，その結合型には生物活性はない．さらに加齢によってSHBG結合型テストステロンが漸増するため，総テストステロンが変化しなくてもBATは相対的に減少する．現在BAT測定は普及していないため，総テストステロン値とSHBGとアルブミンの実測値から計算によって求めた算定(calculated)遊離テストステロンと算定BATを求めることが多い．

### c．副腎ステロイド

副腎アンドロゲンであるdehydroepiandrosterone (DHEA)やDHEA-sulfate (DHEA-S)は加齢により，漸減するので，老化指標の一つであるとともに，LOH症状および徴候を惹起する可能性がある．また，血中コルチゾール(cortisol)は，生涯を通じて変動を認めないが，ストレスで変動することが知られているので，LOH症候群と一過性ストレスとの鑑別に有用である．

## 2 ホルモン補充療法の適応基準値

### a．海外の基準値

LunenfeldらによるISA，ISSAM，EAUのrecommenndationでは，LOHの基準値は総テストステロン8nmol/L (2.31ng/mL)未満とし，正常値を12nmol/L (3.46ng/mL)以上としている．したがって，8nmol/L以上～12nmol/L未満(2.31～3.46ng/mL)をボーダーラインと規定し，これらの症例に算定遊離テストステロンの測定を推奨し，診断と治療のアルゴリズムを作成している[4]．

さらにNieschlagら[5]による詳細な指針によれば，生化学的検査は午前7～11時までに採血をして総テストステロンとSHBGを測定することになっている．このように，海外ではLOH症候群の診断のためのアルゴリズムは総テストステロンを基準としている．

b．わが国の基準値

しかしながら，わが国の健常男性の検討から[6]総テストステロンは加齢による減少がきわめて軽度であり，それに対し遊離型テストステロン値は有意に加齢とともに減少すること（図5），および健康保険の関係で総テストステロンと遊離型テストステロンを同時に測定できないことなどから，**「LOH症候群―加齢男性性腺機能低下症候群診療の手引き」[1]では遊離型テストステロンをLOH症候群の診断検査とすることを推奨している．**

遊離型テストステロン値は一律に平均値で示すことは無理がある．そこでLOH症候群の診断基準

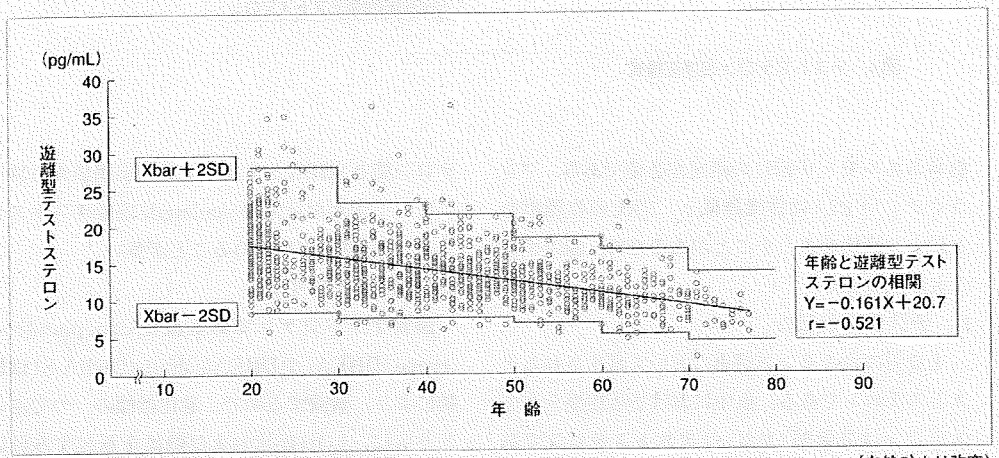


図5　遊離型テストステロン基準値と年齢分布　（文献5）より改変）

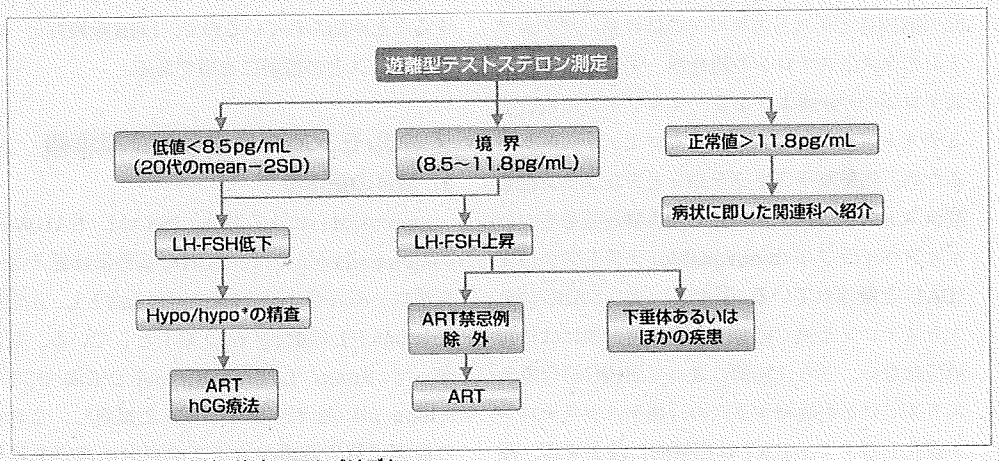


図6　LOH症候群の診断・治療のアルゴリズム
＊Hypo/hypo：hypogonadotropic hypogonadism

値として，図5のデータから20代のmean−2SDである8.5pg/mLを正常下限値とした．さらに，8.5pg/mL以上であっても20代の平均値（young adult mean：YAM）の70%値である11.8pg/mL未満までの症例は，男性ホルモン低下傾向群（LOHのボーダーライン症例）として男性ホルモン補充療法（androgen replacement therapy：ART）の対象とすることが，LOH症候群診断のアルゴリズムとして提案されている（図6）．

## Ⅲ 治療の実際

### 1 男性ホルモン補充療法（ART）の適応

前項で述べた基準に基づき，ARTの適応が以下のごとく決められている．

まず，血中遊離型テストステロンが20代男性のmean−2SDである8.5pg/mL未満の場合，ARTを第一に行う．

遊離型テストステロンがYAM値の70%である11.8pg/mL未満で，かつ8.5pg/mL以上である場合は，男性ホルモン低下傾向群としてARTを考慮する．症状および徴候の程度に応じ，患者にARTのリスクと有用性を説明したうえでARTを治療の一つの選択肢とする．

血中遊離型テストステロン値が11.8pg/mL以上の場合，ARTは行わず，症状の内容により以下の治療を考慮する．性機能症状が強い場合は，PDE5阻害薬を投与する．心理症状が強い場合は，精神神経科医・診療内科医と相談し，抗うつ薬，抗不安薬を投与する．身体症状が強い場合，骨粗鬆症が疑われる場合は，専門医と相談し薬物療法を検討し，筋力低下に対しては生活習慣の改善などを指導する．

### 2 ARTの除外基準

前立腺癌患者や睡眠時無呼吸発作を有する場合はARTを行わない．**PSA値は「LOH症候群—加齢男性性腺機能低下症候群診療の手引き」[1]では2ng/mL以上の場合，ARTを相対的禁忌としている．**そのほか，重篤な内臓疾患を有する患者は除外されている．

### 3 ARTのプロトコル

実際のARTの方法として，わが国では以下の3つが推奨されている．

まず，エナント酸テストステロン筋注であり，1回125mgを2～3週ごと，または1回250mgを3～4週ごとに投与する．

血中LHが正常例に対してはhCG負荷試験を行い，血中テストステロンの反応性が良好であればhCGを投与する．hCG 1回3,000～5,000単位を週1～2回または2週間ごとの筋注が推奨される．

男性ホルモン軟膏は健康保険では使用できないが，OTC薬として市販されている．1回3gを一日1～2回陰嚢皮膚に塗布（1回3mgテストステロン相当）で安定した血中テストステロン濃度が得られる[7]．

## Ⅳ ARTの副作用とその監視

ARTに際し考慮すべきリスクとして，心血管系疾患，脂質代謝異常，多血症，体液貯留，前立腺肥大症，前立腺癌，肝毒性，睡眠時無呼吸症候群，女性化乳房，痤瘡，精巣萎縮，不妊，行動・気分の変化があげられる．

治療開始後の血液検査は2～4週後，3ヵ月後，

6ヵ月後，12ヵ月後，以後は1年ごとに行い，検査値に基づいて治療の中止または適宜投与量の増減を行う．また，適宜専門医に患者の治療を依頼する．

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Review Article

# Late-onset hypogonadism (LOH) and androgens: Validity of the measurement of free testosterone levels in the diagnostic criteria in Japan

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Abstract: The basis of diagnosis of late-onset hypogonadism (LOH) is the measurement of androgen levels. Traditionally, total testosterone (total T) was also used as the primary indicator of gonadal function in Japan. In 1998, the International Society for the Study of the Aging Male was founded to conduct basic and clinical research on this issue internationally. As a result, it is said that bioavailable testosterone levels should be measured in the diagnosis of LOH. At present, however, there are a number of problems for bioavailable testosterone to become a routine diagnostic tool. Here, we will explain the various measurement indicators of androgens, measurement problems, standard values of total T, and free testosterone (free T) in Japan, and the diagnostic methods for LOH overseas. In Japan, the Japanese Urological Association and the Japanese Association of Men's Health recommend the measurement of free T levels in the diagnosis of LOH, for the following reasons: (i) It has been demonstrated that free T is more strongly correlated with calculated bioavailable testosterone, than total T, showing a statistically significant difference; (ii) The behavior of free T is highly consistent with that of bioavailable testosterone, with free T levels being markedly decreased due to aging; (iii) For the measurement of free T, a method that allows the measurement of free T only, without affecting the balance between free T and protein-bound testosterone in blood, is available; and 4) The mean total T by age range decreases only to 80% of the young adult mean even during presenile and senile periods, when LOH occurs most frequently, but the free T level shows a linear decrease with aging and drops to 50% of the young adult mean. For these reasons, we will describe the validity of the recommendation for the measurement of free T levels.

Key words: free testosterone, total testosterone, young adult mean (YAM).

## Introduction

In 2005, the International Society of Andrology (ISA), the International Society for the Study of the Aging Male (ISSAM), and the European Association of Urology (EAU) defined late-onset hypogonadism as 'a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems'.[1–3] More specifically, it requires a diagnosis of hypogonadism requiring clinical treatment to be made in the presence of low androgen levels and signs/symptoms suggesting lack of androgens. The symptom most closely associated with hypogonadism is said to be low libido.[4] Other symptoms associated with hypogonadism include erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality, and impaired mood. These symptoms are not necessarily specific to androgen deficiency but suggest lack of androgens. In other words, a diagnosis of late-onset hypogonadism (LOH) should be made in the presence of at least one of these symptoms with low androgen levels.[5]

Therefore, the basis of the diagnosis of LOH is the measurement of androgen levels. In Japan, as specified in the 'Clinical Practice Manual for Late-onset Hypogonadism Syndrome'[6] it has been decided to recommend the measurement of free testosterone (free T) levels as a diagnostic test for LOH.

In this report, we explain problems in the measurement of androgen levels, methods for determination of normal ranges, diagnostic methods in various countries, and the validity of the reasons for the measurement of free T levels in the diagnosis of LOH in Japan.

## Measurement indicators of androgen, measurement problems, and standard values

### Measurement indicators of androgens

Androgens include dihydrotestosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S), testosterone (T), and dihydrotestosterone (DHT), which are biosynthesized from cholesterol in the adrenal glands and testes. About 98% of testosterone in the blood exists bound to sex hormone-binding globulin (SHBG) (SHBG-bound testosterone [SHBG-T]) and to albumin (albumin-bound testosterone [Alb-T]), and the remaining 2% exists as free T. Since the binding of Alb-T is weaker than that of SHBG-T, testosterone is easily separated from Alb-T. In addition, free T and Alb-T have the biological activity of androgen. Therefore, free-T and Alb-T comprise so-called bioavailable testosterone (BAT).[7–9] In other words, BAT is considered to be the sum of Alb-T and free T other than the SHBG-T fraction, which is precipitated by ammonium sulfate. In the guidelines by Nieschlag *et al.*,[1–3] total T is recognized worldwide as an indicator of androgen in the diagnosis of hypogonadism. Free T calculated from measured total T and SHBG values, or free T measured by reliable free

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testosterone using a dialysis method, has gained a certain reputation as bioavailable testosterone.[10,11] In Japan as well, favorable correlations between BAT and calculated BAT and between calculated free T and free T have been reported,[12,13] and these findings are being further researched in some institutions. However, in Japan, reagents for measurement of SHBG have not been approved as *in vitro* diagnostics and are not covered by health insurance and are therefore not commonly used.

## Age-related changes in androgens

There are various reports on age-related changes in blood androgen concentrations in normal men. The cause of this inconsistency may vary depending on the study population consisting of men who are considered to be normal (men undergoing health checkups, outpatient men who have a disease but maintain high activity levels, or men selected randomly by an epidemiological survey), etc. In other words, there is no uniform definition for normal healthy men. Therefore, attention should be paid in the case of comparison of publications in terms of changes in androgens.

### Age-related changes in total T

Findings from reports on age-related changes in total T vary: some reports have shown marked or moderate decrease, and others have shown no age-related decrease. Purifoy *et al.*[14] measured testosterone in 80 healthy active males aged 20 to 88 years, and showed a tendency toward age-related decreases ($0.05 < P < 0.10$) in testosterone. Morley *et al.*[15] conducted a longitudinal study over a 15-year period in 77 very healthy men aged 61 to 87 years. This investigation demonstrated a statistically significant age-related decrease in testosterone, at a rate of 1.1 ng/mL per decade. Zmuda *et al.*[16] reported a 0.035 ng/mL per year decrease in total T over 13 years of observation in 66 men aged 41 to 61 years. In addition, Harman *et al.*[17] observed a decrease of 0.032 ng/mL (1%) per year in 890 generally healthy men in a cross-sectional study, or even in a longitudinal study. Feldman *et al.*[18] conducted the Massachusetts Male Aging Study (MMAS), which is a longitudinal study conducted over 7 to 10 years in more than 1100 men, and observed a slightly progressive decrease at a rate of 1.6% per year. However, the rate of decrease in a cross-sectional study was 0.8% per year. On the other hand, Jensen *et al.*[19] conducted a cross-sectional study in 924 randomly selected healthy men. They reported that there was no age-related decrease, with no differences in total T or in free androgen index ([testosterone/SHBG] × 100) between elderly people and non-elderly people. Also in Japan, there is a tendency toward age-related decreases in total T, but there is no statistical significance, as described later.

### Age-related changes in free T

A consistent result showing age-related decreases in free T was obtained in a number of reports from cross-sectional studies. The percentage of age-related decrease is known to be significantly higher in free T than in total T. The cause of this may be that SHBG levels increase with age. A statistically significant decrease in free T was also observed in Japanese studies. Also in the longitudinal study by Harman *et al.*,[17] age-related decreases in free T index (a calculated value related to free or bioavailable T) were observed.

## Measurement problems

Blood Sampling Time Points. Androgens exhibit diurnal variation, beginning to decrease in the afternoon. In the guidelines by Nieshlag,[1-3] it is recommended to collect blood samples for androgens and SHBG during the period from 7.00 hours to 11.00 hours. In a study by the author *et al.*,[20] total T and free T were measured in three healthy male volunteers by collecting blood samples over time from awakening to bedtime. In the study, both parameters showed a marked diurnal rhythm, remaining high and relatively stable in the morning, followed by a decrease during the afternoon, with a nadir before bedtime. These findings suggest that stable results can be obtained with blood samples collected in the morning. In particular, precaution should be exercised in younger people, because they show marked diurnal variation.

Measurement Differences Among Assay Kits. In the measurement of total T, it should be kept in mind that values determined using various commercially available assay kits do not necessarily agree. Boots *et al.*[21] evaluated the between-kit variability and precision of six different commercially available testosterone assays. Their data showed most commercially available kits for measuring the total T level demonstrated significant between-kit variability, and they concluded the measurement of total serum testosterone using commercial kits may have limited utility. Therefore, the manufacturer of the kit used should be identified, in the case of using overseas standard values for total T and free T (described below) or the lower limit of the standard values for indication of androgen replacement therapy.

## Establishment of standard values of total T and free T in Japan

The normal ranges of total T and free T in Japanese males have been reported by many researchers. However, although the assay kits from DPC are used in many institutions, the normal ranges are not necessarily uniform. In addition, the normal range for free T, proposed by DPC (USA), has been changed three times over the past 10 years or so, even though the kit remains the same. As causes of this, the following were observed in the establishment of normal ranges: a small sample size, bias in age distribution, inconsistent blood sampling time points, inconsistent storage conditions of blood samples collected, and possible ethnic differences. In addition, there were concerns about the validity of not only the standard values but also measured individual values. The tracer in the free T assay kit from DPC is an iodinated testosterone derivative (iodinated 6-hydroxytestosterone-19-carboxymethyl ether histamine). Since it is a derivative, it does not replace testosterone that is bound to SHBG or Alb-Tumin, and only unbound (free) T in the sample and the iodinated testosterone derivative are competitively bound to the immobilized testosterone antibody. On the other hand, the immobilized testosterone antibody has lower affinity for testosterone than Alb-Tumin and SHBG. This prevents the binding of the immobilized testosterone antibody to bound T. Thus, the iodinated testosterone derivative is used[22] to provide a radioimmunoassay (RIA) system using a simple principle that allows only the recognition of free T in the sample. However, since it is a simple measurement system without stringent fractionation of bound and unbound forms, the system has not gained international recognition as a standard measurement system. Under this circumstance, a project for the establishment of standard values of total T and free T in Japanese adult men was launched by the Free T Review Committee, with the approval of the Scientific Committee of the Japanese Urological Association. In 2004, standard values were established and published in the Journal of the Japanese Urological Association. A summary is provided below.[20]

Subjects and Method. Among 1172 adult men who were living healthy lives, 1143 subjects aged 20 to 76 years with serum luteinizing hormone (LH) concentrations within its standard range (for 20 to

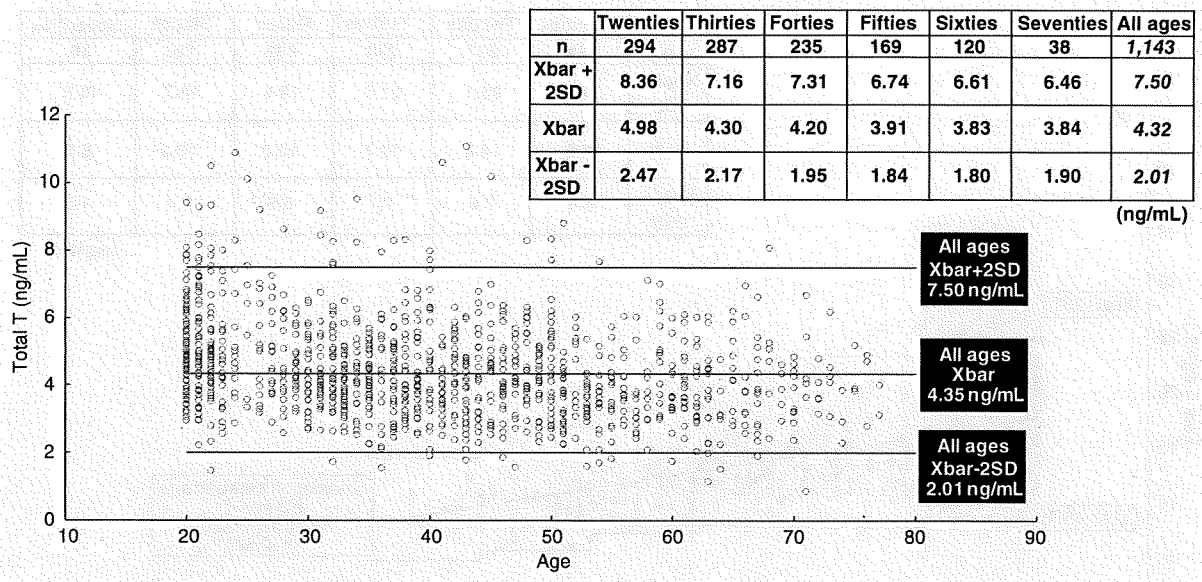


**Fig. 1** For total testosterone, statistical analysis was performed on the data from all subjects aged 20 to 77 years, and the standard range was defined as Xbar ± 2SD. The upper limit (Xbar + 2SD) and lower limit (Xbar − 2SD) were 7.50 ng/mL and 2.01 ng/mL, respectively, with a mean (Xbar) of 4.35 ng/mL.

70 years old: 1.1 to 25.9 mIU/mL) were selected. Blood samples were collected in the morning when total T and free T levels remained high and relatively stable. Separated serum samples were stored at −20°C until assay. Both total T and free T were measured by RIA, using the DPC Testosterone Kit (Mitsubishi Kagaku Iatron) and DPC Free Testosterone Kit (Mitsubishi Kagaku Iatron), respectively. In consideration of the influence of aging, statistical analysis, for either total T or free T, was conducted on all data combined and on data by age group defined by 10-year intervals. The standard ranges were obtained from mean ± 2 standard deviation (2SD), after testing the distribution of measured values in each group and transforming the data into the optimal normal distribution on the histogram. The normality was examined using skewness, kurtosis, and histograms.

Standard Total T Values. Total T showed a tendency toward slight decrease [$y = -0.027x + 5.5$ ($r = -0.276$)] with age, but remained consistent with little change in subjects aged 50 and above. Therefore, it was determined unnecessary to establish standard total T values for each age group, and statistical analysis was performed on all the measured values combined. As a result, the histogram of total T in subjects aged 20 to 70 years corresponded to a square-root distribution, and the standard range obtained from mean ± 2SD was 2.01 to 7.50 ng/mL (mean: 4.32 ng/mL; $n = 1143$) (Fig. 1).

Standard Free T Values. Free T decreased with age, showing a strong correlation with age. The correlation was expressed as $y = -0.161x + 20.7$ ($r = -0.521$), and the rate of decrease was −1.61 pg/mL (−9.2%) per decade. Therefore, standard free T values were established for each age range by 10-year intervals. All the optimal histograms for the age groups corresponded to a square-root distribution. As a result, the normal ranges obtained from mean ± 2SD were 8.5 to 27.9 pg/mL (mean: 16.8 pg/mL; $n = 294$) in the 20s age group, 7.6 to 23.1 pg/mL (mean: 14.3 pg/mL; $n = 287$) in the 30s age group, 7.7 to 21.6 pg/mL (mean: 13.7 pg/mL; $n = 235$) in the 40s age group, 6.9 to 18.4 pg/mL (mean: 12.0 pg/mL; $n = 169$) in the 50s age group, 5.4 to 16.7 pg/mL (mean: 10.3 pg/mL; $n = 120$) in the 60s age group, and 4.5 to 13.8 pg/mL (mean: 8.5 pg/mL; $n = 38$) in the 70s age group.

In this age range, the upper and lower limits of the standard range by age group changes from 27.9 to 13.8 pg/mL and from 8.5 to 4.5 pg/mL, respectively, showing that the rate of decrease is about 50% for both limits. However, when compared in absolute values, the upper limit of the standard range shows a large decrease of −14.1 pg/mL over a period of 60 years, whereas the lower limit of the standard range shows a small decrease of −4.0 pg/mL, with the mean lower limit of the standard values being 6.8 pg/mL (Fig. 2). The standard values established this time are in good agreement with those established by Ooi *et al.*[23] using the same assay kits from DPC. It is particularly interesting that the standard free T values in the respective age groups are in good agreement between Japanese and Westerners, although they have different physiques and lifestyles, such as dietary habits.

Examination Based on the Young Adult Mean. Sato *et al.*[24] have reported that, regarding the relationship between LOH and free T, abnormally low free T values are not necessarily consistent with clinical symptoms, even taking into consideration the standard values by age group. More specifically, they point out that patients with LOH do not necessarily have low testosterone levels. To resolve this issue, the Free-T Review Committee proposed an approach using the young adult mean (YAM) percentage as an indicator of the free T level currently maintained in comparison with the young adult level. As the effect of the age-related decreases in the standard values is more marked for free T than for total T, it is possible to detect an abnormal value with assessment using the YAM percentage, even within the standard ranges of total T and free T.

The YAM is already applied in routine clinical practice for the evaluation of bone mineral density in osteoporosis based on evidence-based medicine.[25,26] The YAM for total T and free T, calculated as means from young adults aged 20 to 39 years, were 4.53 ng/mL and 15.2 pg/mL, respectively. Using the YAM percentage obtained by dividing measured individual values by the YAM, changes in the standard values by age group were examined (Fig. 3). The results showed that the lower limit of the standard range of total T decreased to about 80% in men in their 50s, and then remained almost unchanged in older men up to their

| | Twenties | Thirties | Forties | Fifties | Sixties | Seventies |
|---|---|---|---|---|---|---|
| n | 294 | 287 | 235 | 169 | 120 | 38 |
| Xbar + 2SD | 27.9 | 23.1 | 21.6 | 18.4 | 16.7 | 13.8 |
| Xbar | 16.8 | 14.3 | 13.7 | 12.0 | 10.3 | 8.5 |
| Xbar - 2SD | 8.5 | 7.6 | 7.7 | 6.9 | 5.4 | 4.5 |

(pg/mL)

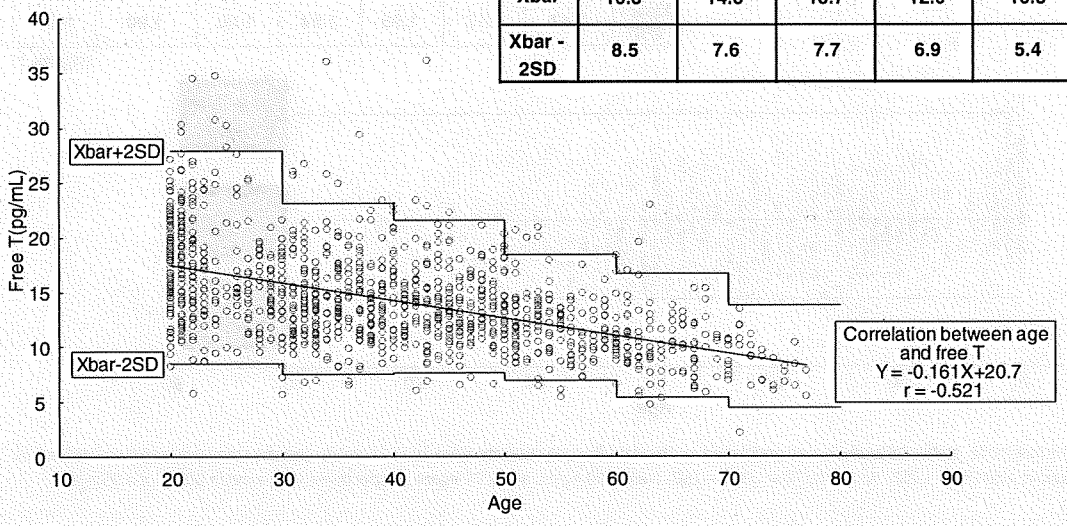


**Fig. 2** For the analysis of free testosterone, all subjects aged 20 to 77 years were divided into age groups defined by 10-year intervals, and statistical analysis was conducted on data by age group. The standard range for each age group was defined as Xbar ± 2 standard deviation. A tendency toward gradual decrease with advancing age was observed. (Standard values by age group are displayed in the table within the figure.)

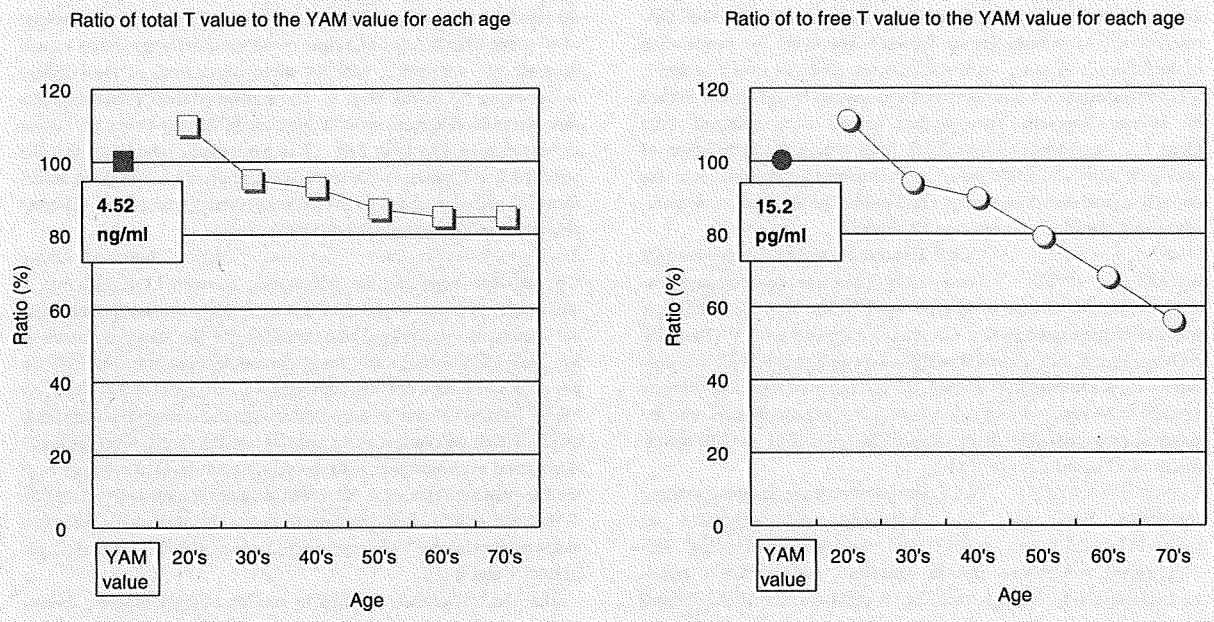


**Fig. 3** In the standard values (mean) by age group, the total testosterone percentage compared to the young adult mean decreased to about 80% in men in their 50s, and then remained almost unchanged thereafter, whereas an almost linear decrease to 56% in free testosterone was observed in men up to their 70s.

70s, whereas an almost linear decrease to 56% in free T was observed in men up to their 70s. Therefore, it is determined to adopt free T levels in the diagnosis of LOH, and the normal lower limit was set at a mean–2SD value of 8.5 pg/mL for men in their 20s. It has been proposed that patients with values of not less than 8.5 pg/mL and less than 11.8 pg/mL, which is 70% of the mean value for men in their 20s, are to be indicated for androgen replacement therapy (ART) as LOH borderline cases.