Hypogonadism in Men Consuming Sustained-Action Oral Opioids

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Abstract: Naturally occurring opiates (endorphins) diminish testosterone levels by inhibiting both hypothalamic gonadotrophin releasing hormone production and testicular testosterone synthesis. Heroin addicts treated with a single daily dose of methadone and nonaddicts receiving continuous intrathecal opioids quickly develop low luteinizing hormone and total testosterone levels. A similar pattern was sought in men consuming commonly prescribed oral opioids. Free testosterone (FT), total testosterone (TT), estradiol (E_2), dihydrotestosterone (DHT), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured in 54 community-dwelling outpatient men consuming oral sustained-action dosage forms of opioids several times daily for control of nonmalignant pain. Hormone levels were related to the opioid consumed, dosage and dosage form, nonopioid medication use, and several personal characteristics and were compared with the hormone analyses of 27 similar men consuming no opioids. Hormone levels averaged much lower in opioid users than in control subjects in a dose-related pattern ($P < .0001$ for all comparisons). FT, TT, and E_2 levels were subnormal in 56%, 74%, and 74%, respectively, of opioid consumers. Forty-eight men (89%) exhibited subnormal levels of either FT or E_2. Either TT or E_2 level was subnormal in all 28 men consuming the equivalent of 100 mg of methadone daily and in 19 of 26 (73%) consuming smaller opioid doses. Eighty-seven percent (39 of 45) of opioid-ingesting men who reported normal erectile function before opioid use reported severe erectile dysfunction or diminished libido after beginning their opioid therapy. Commonly prescribed opioids in sustained-action dosage forms usually produce subnormal sex hormone levels, which may contribute to a diminished quality of life for many patients with painful chronic illness.

Key words: *Hypogonadism, opioids, pain/drug therapy, estradiol, androgen, gonadotrophins, impotence, gonadorelin.*

Men consuming therapeutic opioids several times daily for treatment of chronic pain frequently develop erectile dysfunction, decreased libido, fatigue, and depression.[29,34] These symptoms are usually explained on the basis of the direct pharmacologic action of their opioids, their continuing pain or disability, the underlying disease processes for which analgesics are being administered, personality disorders, or psychiatric disease.[29,34] For several decades, testosterone deficiency has been documented in patients being treated for heroin addiction with methadone[3,8,22,39,40] or acetylmethadol.[23,24] Factors contributing to this deficiency include drug-induced inhibition of the production and release of gonadotrophin releasing hormone (GnRH)[11,17,27,31,37,41] and opioid-induced inhibition of testicular testosterone synthesis.[2,7,36] Several groups of investigators have recently demonstrated severe hypogonadism in the small population of men and women treated with intrathecal opioids for control of chronic pain.[1,14,25]

Use of sustained-action opioids in the treatment of chronic persistent pain and in the treatment of heroin addiction has rapidly expanded in recent years, with many patients now consuming multiple doses of these medications daily for a period of many years.[19]

Hypogonadism induces many physiologic changes in addition to its influence on sexual interest and function, depression, and energy level. These include muscle wasting and osteoporosis[4,20,28,35] and may include lowered pain threshold[15,26] and impaired wound healing.[5,16] Diminished testosterone levels characteristically begin within 4 or 5 hours after ingestion of a single morning methadone pill during treatment for heroin addiction.[3,8,22-24,39,40] Even though a potential relationship has been recognized between this narcotic-induced hypogonadism and the impotence of these patients,[3,29] hormone replacement therapy in these or other patients receiving oral opioids has apparently not been suggested. In contrast, the patients receiving intrathecal opioids reported by Abs et al[1] and Paice et al[25] often lost many of their hypogonadal symptoms during appropriate replacement therapy.

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The severity and frequency of opioid-induced androgen deficiency (OPIAD) in community-dwelling patients consuming daily prescribed analgesics have not previously been examined. After our preliminary observation suggesting a high frequency of OPIAD among these patients in our community[10] and a dramatic improvement in some during appropriate hormone replacement, additional studies were undertaken.

Methods

Physicians in our rural community of 80,000 people were invited to refer opioid-consuming men and women for hormone analysis. Eligibility criteria included daily consumption of at least 20 mg of hydrocodone for 2 or more weeks or the analgesic equivalent of another opioid, the absence of hospitalization within the preceding 2 months, and absence of a prior diagnosis of hormone deficiency, prior pelvic or testicular therapeutic radiation, chronic liver or kidney disease, a history of malignancy requiring systemic therapy, and prior ovarian or testicular surgery.

Participants completed a questionnaire designed for our study that was completed in private by each subject and returned, usually by mail, to the investigator. Data requested included medical history, current medication consumption, diagnosis requiring the use of analgesics, changes in sexual function since beginning opioid usage, and tobacco and alcohol usage. Subjects were specifically asked to compare their present sexual interest and performance with that before the onset of daily opioid administration. The present report includes data from the first 54 men referred for analysis who were consuming sustained-action oral dosage forms of opioid several times daily. Analgesic doses were converted to methadone equivalents by using the analgesic equivalents of each of the opioids represented in our subjects, as previously compared by McRae and Sonne.[21] Hydrocodone 15 mg, oxycodone 15 mg, morphine sulfate 15 mg, methadone 10 mg, and codeine sulfate 100 mg were considered to be equivalent. Single blood samples were obtained between 6:30 am and 6:00 pm without regard to the time of prior ingestion of food, fluid, or medication.

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and estradiol (E_2) levels were measured by radioimmunoassay (RIA) at a local commercial laboratory. Total testosterone (TT) and dihydrotestosterone (DHT) levels were determined by RIA and free testosterone (FT) level by equilibrium dialysis at a reference laboratory after transport by overnight courier. FT levels were compared with the average FT values for 10-year age groups reported by Vermeulen et al,[38] who used an analytical technique similar to that of our reference laboratory.

Changes in FT levels during daytime hours have apparently not been reported. For analysis by time of blood collection, our subjects' FT levels were compared with average hourly FT levels determined by multiplying the hourly average TT levels reported by Bremner et al[6] for men who were younger (age, 23 to 28 years) or older (age, 58 to 82 years) than our subjects by the FT/TT ratios established by Vermeulen et al[38] for men of comparable age (.02 for men 23 to 28 years old and .013 for men 58 to 82 years old).

DHT and E_2 values reported as below the lower limit of reliable quantitation ($<$6 ng/dL and $<$10 pg/mL, respectively) were included in averages as half of this lower limit of reliable measurement.

Hormone values were compared with those of 27 community-dwelling men from my private practice of internal medicine, all of whom fulfilled all criteria for inclusion in the study except for opioid ingestion. Most of these had rarely consumed opioids, none had a history of habitual opioid consumption, and none had ingested opioids during the week before analysis.

Analysis of similar studies in opioid-consuming women and in men consuming either short-acting oral opioids or opioids by transdermal or intravenous routes will be reported separately.

The study was approved by the Institutional Review Boards of Mercy Medical Center and Redding Medical Center, the 2 community hospitals in our city. Probabilities were determined by the chi-square test.

Results

Twenty-four subjects were consuming methadone in multiple daily doses, 18 subjects were consuming sustained-action oxycodone, and 12 were consuming sustained-action morphine sulfate. Eleven men also consumed smaller doses of short-acting tramadol, oxycodone, or hydrocodone daily in addition to their sustained-action narcotic. The analgesic equivalent of these short-acting opioids was included in the dose-related analysis of our results.

Characteristics of our 54 subjects are presented in Table 1. A majority of subjects were being treated for chronic back pain, many had undergone multiple cervical or lumbar spine operations, and most had developed severe erectile dysfunction since beginning opioid use. Fifty were white and 4 were Spanish-American. Although related data were not available for many subjects, 5 were known to have had failed spinal fusions and 3 to have had femoral or vertebral osteoporotic fractures documented by appropriate bone mineral density determinations after years of analgesic ingestion.

Table 2 presents average hormone values for men consuming differing daily narcotic doses. In comparison with control subjects, values for each hormone analyzed were much lower ($P < .0001$) in opioid-consuming subjects in a dose-related pattern. FT, TT, E_2, and DHT values were less than normal in 56%, 74%, 74%, and 81%, respectively, of subjects. Of the 22 men with FT levels within the normal range, 16 had subnormal E_2 levels, leaving 6 (11%) in whom FT and E_2 levels were both normal. Of the 13 with normal TT levels, 6 had subnormal E_2 level, leaving 7 of the 54 (13%) with both levels normal. All 28 men consuming the equivalent of 100 mg or more of methadone daily had either TT or E_2 level or both of them below

normal. Twenty-seven of the 28 had either FT or E_2 level or both of them below normal.

Fig 1 presents LH and FT values for both opioid-consuming and control subjects. Fig 2 provides a similar presentation of LH and TT values. Almost all LH values in opioid patients were inappropriately low for the low levels of FT and TT. Fig 3 relates FT to each subject's age in comparison with the average FT levels reported by Vermeulen et al.[38] Fig 4 relates FT levels to the hour of blood sampling and compares these values with calculated average FT levels for 2 groups of men who were younger and older than most of our opioid-consuming subjects. In our subjects, FT levels were largely independent of both age and time of day. In control subjects, TT and FT levels were higher in the 5 men younger than age 50 than in those older than age 50 and were 10% to 15% higher in morning specimens than in afternoon specimens.

The dose-related pattern of lower hormone levels in opioid consumers was similarly present in blood specimens obtained during morning and afternoon hours.

Hormone values did not differ between men consuming different forms of sustained-action analgesics in comparable doses and were unrelated to the frequency of opioid ingestion. Hormone values were unrelated to smoking habits, alcohol use, and the use of antidepressants or antiseizure medications. Hormone values were unrelated to height, weight, and body mass index (BMI), except that E_2/TT ratios were higher in obese men and lower in underweight men. Development of erectile dysfunction since the onset of opioid therapy was unrelated to opioid dose, the use of antidepressant or antiseizure medication, FT or TT levels. Examination for these potential associations was handicapped, however, by the small number of opioid consumers who had not developed erectile dysfunction.

Discussion

Our data demonstrate a high frequency of apparently symptomatic hypogonadotropic hypogonadism in community-dwelling men consuming multiple daily doses of commonly prescribed opioids. Our observations, to-

Table 1. Characteristics of Subjects

	Opioid Patients	*Control Patients*
No.	54	27
Average age (y) (range)	49.9 (30-78)	57.4 (40-67)
Habitus		
Underweight (BMI, <20)	4 (7%)	3 (11%)
Normal (BMI, 20-27)	27 (50%)	18 (67%)
Average (BMI, >27)	23 (43%)	6 (22%)
Subnormal hormone levels		
Free testosterone*	30 (56%)	1 (4%)
Total testosterone*	40 (74%)	2 (8%)
Dihydrotestosterone*	44 (81%)	7 (26%)
Estradiol*	40 (74%)	6 (22%)
Smokers, current	15 (28%)	5 (19%)
Antidepressant medication	23 (43%)	6 (22%)
Anticonvulsant medication	5 (10%)	2 (8%)
Duration of opioid use		
Under 1 y	7	
1-5 y	22	
6-10 y	19	
>10 y	6	
Daily opioid use (methadone equivalents)		
20-39 mg	8	
40-60 mg	7	
70-120 mg	23	
130-240 mg	14	
>240 mg	2	
Sexual Function		
Impotent since before opioid	5	
Change since beginning opioid		
Normal function continues unchanged	6	
Intermittent erectile dysfunction or decreased libido	5	
Consistent erectile dysfunction	34	
Unknown	4	
Illness requiring opioids		
Back pain	42	
Other orthopedic problems	4	
Headaches, neuritis, other	8	

*$P < .0001$.

Table 2. Average Hormone Levels in Men Consuming Sustained-Action Opioids in Multiple Daily Doses

Methadone equivalents (daily consumption)	*No. of men*	*Age average (years)*	*Testosterone*		*DHT (ng/dL)*	*LH (mIU/mL)*	*FSH (mIU/mL)*	*Estradiol (pg/mL)†*
			Free (pg/mL)	*Total* (ng/dL)*				
0	27	57.4	127.4 (±48.8)	449.1 (±181.1)	39.3 (±22.3)	6.1 (±3.5)	8.8 (±8.5)	32.0 (±17.2)
20-60 mg	15	51.9	74.3 (±43.5)	265.8 (±191.9)	20.4 (±11.6)	4.6 (±2.5)	8.1 (±7.5)	18.7 (±8.4)
70-120 mg	23	49.4	41.7 (±25.5)	188.5 (±193.4)	17.6 (±16.7)	4.6 (±3.1)	4.7 (±4.3)	14.7 (±8.9)
>120 mg	16	47.8	44.8 (±26.3)	172.1 (±108.8)	15.0 (±9.7)	2.4 (±1.3)	4.3 (±2.4)	11.7 (±6.3)
Normal range			50-210	260-1000	25-75	2-18	1.6-18.1	21-50

Abbreviations: DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

NOTE. Figures in parenthesis indicate standard deviation of each mean.

*Conversion factor to nmol/L = 0.0347.

†Conversion factor to pmol/L = 3.671.

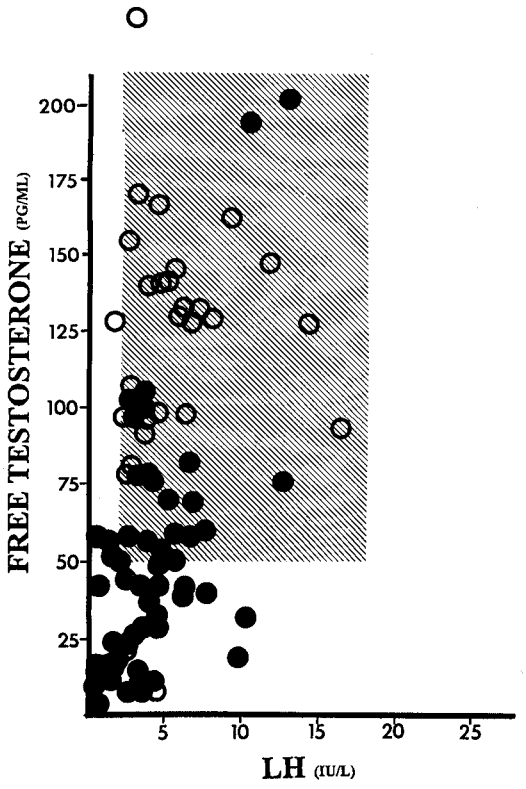

Figure 1. LH and FT values for 54 men consuming sustained-action oral opioids (closed circle) and 27 control subjects (open circle). Shaded area indicates the normal range of values for both hormones

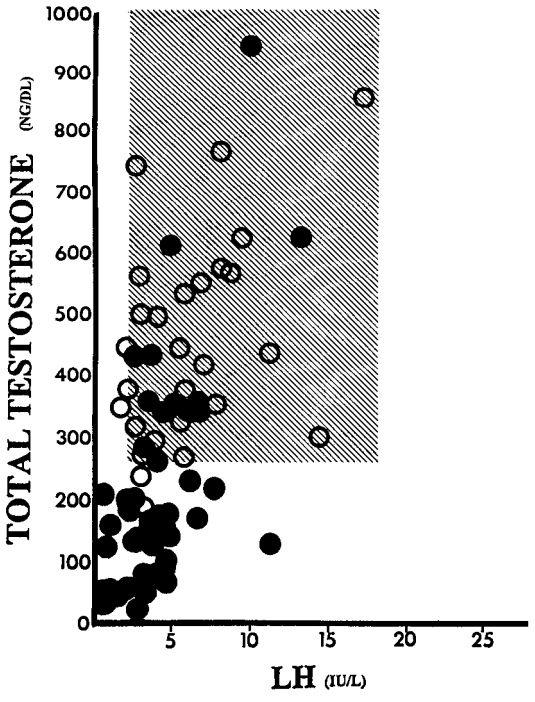

Figure 2. LH and TT values for 54 men consuming sustained-action oral opioids (closed circle) and 27 control subjects (open circle). Shaded area indicates the normal range of values for both hormones

gether with those of others, strongly suggest that this easily treated and largely unrecognized complex of hormone deficiencies is opioid induced and is probably present in large numbers of men in most communities.

OPIAD appears within a few hours of analgesic ingestion. Mendleson et al[23] documented an average drop in TT level to less than 50% of normal baseline within 7 to 9 hours after oral ingestion of a single dose of 30 to 80 mg of acetylmethadol in heroin addicts treated with this medication. TT levels dropped to castrate levels in several subjects, remaining low for more than 24 hours after ingestion but returning to baseline by 48 to 72 hours after ingestion. Similar observations of shorter duration after oral ingestion of 30 or more mg of methadone were made by Woody et al.[40] In their patients TT levels were still decreasing 51/2 hours after ingestion but usually had returned to baseline within 24 hours if ingestion had been limited to 60 mg or less. In contrast, baseline TT levels were much lower (and frequently below normal) in men receiving a single daily methadone dose of 80 mg or more,[22] reflecting incomplete recovery of androgen depression 24 hours after ingestion. Vescovi et al[39] reported low morning TT and LH values in 15 young men receiving 20 mg of methadone twice daily as treatment for heroin addiction. The postingestion drop in TT was strongly dose-related in the few subjects in whom this relationship has been examined.[22] TT levels apparently return to normal within a few days after opioid withdrawal even after prolonged use.[22,40]

A variety of studies support a prominent contribution to OPIAD by the inhibiting influence of these analgesics on the pulsatile generation of GnRH within the hypothalamus and its release into the venous channels by which it is transported to the pituitary gland. GnRH pro-

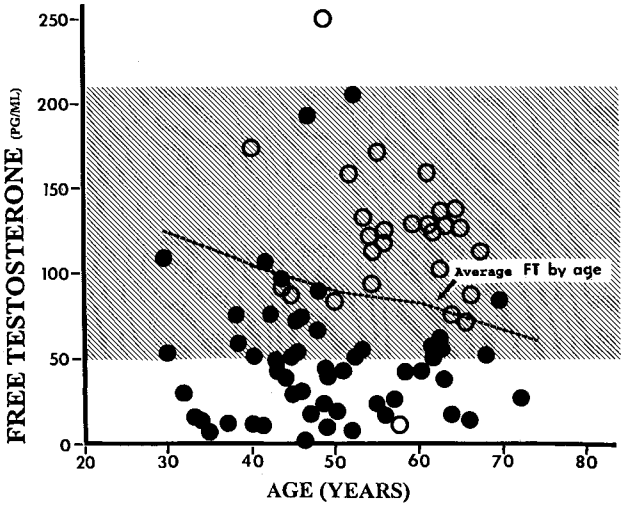

Figure 3. FT values for 54 men consuming several daily dosages of sustained-action oral opioids (closed circle) and 27 control subjects (open circle) presented by age at the time of analysis. Shaded area indicates normal FT range. Dotted line indicates average FT for age.[30]

duction is naturally inhibited by endorphins and greatly stimulated by opoid antagonists. GnRH, LH, and TT levels were all substantially increased by administration of the opioid antagonist naltrexone,[11,17,31] a pattern that has been documented in both humans[11,37] and rats.[31] Similarly profound decreases in the levels of GnRH,[31,41] LH,[27] and TT[22,40] followed administration of either morphine sulfate or methadone in humans[22,40] and in rats.[31,41] Opioid-consuming subjects in our study almost universally exhibited LH values that were inappropriately low considering their low FT and TT values, a pattern compatible with an inhibiting influence on GnRH production by their ingested analgesics.

A portion of the opioid influence on GnRH production may be mediated through the increased prolactin levels characteristic after opioid administration.[12,39,40] Men with prolactinomas and high prolactin levels characteristically have low testosterone levels, largely resulting from prolactin-induced inhibition of GnRH formation. Elevated prolactin levels may also directly inhibit testicular testosterone production.[18] We did not measure prolactin levels in our subjects, but several observations suggest that profoundly diminished sex hormone levels would have been present, independent of any influence by increased prolactin. In the hypogonadal men identified during intrathecal opiate administration reported by Abs et al,[1] prolactin levels were only 38% higher than in their control subjects (average values, 6.8 vs 4.9 μg/L), and almost all values in their patients receiving opioids remained within the normal range. The substantial increases in testosterone in response to opioid antagonists[11,17,31,37] showed the sensitivity of GnRH production to the influence of opioid receptors.

Other evidence supports the possibility of contributions to OPIAD by opioid influence within pituitary and testicular tissues. Opioid receptors have been reported in canine pituitary glands,[30] an observation compatible with opioid inhibition of LH production within the hypophysis. Tinajero et al[36] demonstrated a dose-related decrease in testosterone production by Lehdig cell cultures in response to β-endorphins. Adams et al[2] documented decreased concentrations of testosterone in testicular interstitial fluid of rats 1 to 6 hours after morphine administration and increases in these levels after injection of the opioid antagonist naloxone, both changes being independent of the effects of LH. Chadnrashekar and Bartke[7] similarly demonstrated decreased testosterone formation in response to β-endorphin administration in hypophysectomized rats.

Most male estrogen is formed in adipose tissue in which aromatase catalyzes the metabolism of testosterone into E_2. The higher E_2/TT ratios in our more obese subjects and the lower E_2/TT ratios in our underweight patients confirmed this pattern, previously reported by others.[13]

In younger normal men, FT levels exhibit a circadian pattern, with highest average levels during the early morning hours and average levels progressively lowering throughout the daytime hours. Superimposed on this cycle are frequent surges in TT and FT levels, which may

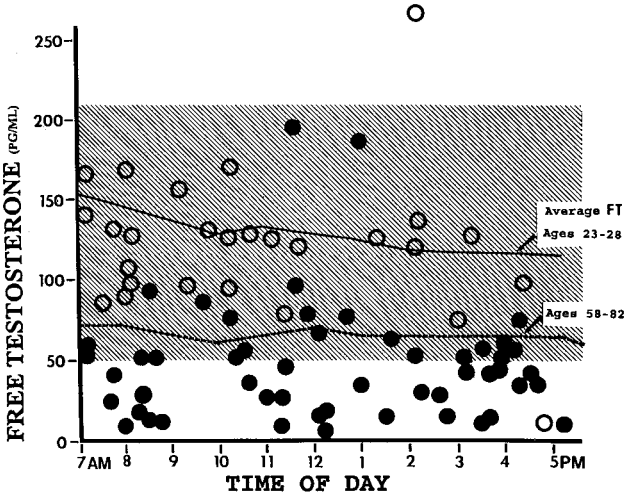

Figure 4. FT values of 54 men consuming sustained-action oral opioids (closed circle) and 27 control subjects (open circle), presented by hour of blood analysis. Shaded area indicates normal FT range. Lines indicate estimated average normal values for time of day in younger and older men (data from references 31 and 30.)

increase by 30% to 40% in a few minutes in response to even greater surges in LH or decrease by a similar amount in less than an hour, reflecting the 30-minute half-life of testosterone. The absence of higher testosterone levels during morning hours in our subjects suggests that opioids may inhibit factors responsible for this diurnal testosterone pattern. A pattern of wide fluctuations in testosterone levels within a short period of time may have contributed to the atypically high levels determined in a few opioid-consuming men and to the very low levels exhibited in some men consuming small opioid doses.

In contrast to the wide fluctuations in testosterone levels characteristic of younger normal subjects, E_2 levels exhibited much less diurnal change.[13] This difference reflects, in part, the 4-hour half-life of this estrogen. In the 22 opioid-consuming subjects with normal FT levels, these FT levels were usually near the lower normal limit. Sixteen of these 22 had subnormal E_2 levels at the time of blood analysis, suggesting that analysis may have been obtained near a peak testosterone level, with recorded FT levels higher than those present during much of the day. Similarly, the 5 men whose FT levels were below normal, but estrogen levels within normal limits, often had E_2 levels near the low normal limit, suggesting that the low FT levels may have been obtained at a low nadir of testosterone. This pattern of low normal E_2 and subnormal testosterone was shown to be a common pattern in 1 small series of young men not consuming analgesics and without symptoms of hypogonadism.[33] These observations suggest that the combination of FT or TT and E_2 levels may be useful in diagnosing mild hypogonadism, but that even this combination of hormone values determined from a single blood sample is unlikely to be sufficient to establish a diagnosis of hormone deficiency whether the pattern is opiate induced or not.

Average FT levels progressively diminish after early

adulthood. Factors contributing to this decline probably include decreases in the numbers and responsiveness of Lehdig cells as well as those cells producing GnRH and LH. Although the responsiveness of the hypothalamus to endorphins greatly diminishes with advancing age, our data show prominent OPIAD in older as well as young men, supporting the persistence in older men of a prominent inhibitory influence by opioids on the cascade of reactions contributing to testosterone formation.

Our control patients differed from our opioid-consuming subjects in several ways. Fewer of them were using antidepressant medications; they were older and were less often obese. These differences seem likely to have contributed little to the hormonal differences between our control and study groups. Although antidepressants and anticonvulsants may cause sexual dysfunction, their use by our opiate-consuming subjects was not associated with a greater frequency of erectile dysfunction than was present in other opiate consumers. None of the antidepressants consumed by our subjects has been shown to alter sex hormone levels. Sex hormone levels in our subjects were independent of their use both among our control subjects and among our opiate-consuming subjects.

Prominent obesity generates increased E_2 and lowered TT levels. Although the greater frequency of obesity among our opiate consumers may have contributed to their lower FT and TT levels, it would be expected to make less apparent any opiate-induced drop in E_2 levels. In spite of any influence by obesity on E_2 levels, these levels were strikingly lower in obese opiate consumers than in control subjects in a dose-related pattern similar to that of nonobese opiate users.

Although TT levels change little with advancing age in most studies, average FT levels are lower in older men, suggesting that adjustment for the older average age of our control patients would have resulted in even larger differences between the FT levels of control subjects and opiate-consuming subjects.

Morning testosterone levels in men are characteristically higher than these levels obtained later in the day. TT and FT values from our 11 control subjects whose analysis was obtained after 11:00 am were 10% to 15% lower than the 16 values obtained before this time, a difference that was smaller in older than in younger men. These small differences and the absence of a diurnal pattern in opiate-ingesting men suggest that blood analyses limited to the morning hours would have had little influence on the results we report. This assumption is supported by the similar pattern in morning and afternoon hormonal differences between control and analgesic-consuming subjects.

Male estrogen has recently been recognized as being more important physiologically than previously thought. Low levels may contribute prominently to the osteoporosis of male hypogonadism.[4,20,28,35] The presence of premature osteoporosis manifested by osteoporotic fractures in several of our men younger than age 60 is compatible with OPIAD-induced osteoporosis in them.

More than 120,000 patients are currently receiving sustained-action opioids in federally licensed heroin treatment centers in the United States; our observations strongly suggest that many of these patients have unrecognized and untreated OPIAD. The possibility of a contribution to prevention of relapse in these patients by correction of any documented hypogonadism should be evaluated.

Hypogonadism is a major cause of osteoporosis in men[4,20,28,35] as well as in women. During the first 2 years after surgical or chemical castration, men lose an average of 3% to 5% per year of their bone mineral density[9,32] for at least the first 2 postcastration years, a rate that is more than 6 times normal. Their bone loss has been reported to continue at a faster than normal rate for at least 6 more years.[9] These observations, as well as the history of osteoporotic fractures in several of our subjects with OPIAD, present evidence favoring a greatly increased risk for osteoporotic fractures among many men consuming opiates for many years. Whether treatment of their hypogonadism will prevent associated osteoporosis in men with OPIAD should be examined by appropriate studies.

A lower pain threshold developed gradually in male rats during the 3 weeks after castration,[15,26] returned thereafter to normal during a similar period in animals receiving adequate testosterone replacement, but remained low in animals receiving placebo. These observations are compatible with lower opiate requirements in men with OPIAD during hormonal replacement to physiologic levels.

Studies showing less effective wound healing in hypogonadal animals[5,16] suggest the possibility of improved wound healing in men with postoperative or post-traumatic OPIAD who receive replacement testosterone.

We did not incorporate into our study any of the standard protocols for assessing symptoms of hypogonadism. Data from one or more of these devices would have complemented the observations we report, and several are included in our ongoing studies. Abs et al[1] and Paice et al[25] reported striking improvement in many of their men receiving testosterone replacement for hypogonadism induced by intrathecal opioids. Their observations suggest that similar benefit may be common in men who develop OPIAD during oral opioid therapy and indicate the urgent need for studies that should help to define the most effective technique for identifying and treating this common disorder.

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