News and Views

High FT4: A Risk Factor for Mortality in Older Men

Serum free thyroxine (FT4) is an independent predictor of adverse health outcomes and mortality risk in older men, according to findings of a study from Sweden published in the *Journal of the Endocrine Society*[1].

The prospective, population-based study was conducted to examine if serum FT4 or thyroid-stimulating hormone (TSH) could predict mortality, cardiovascular disease (CVD), or cancer risk in older men. A total of 1,801 Swedish men, mean age 75 years, from the Gothenburg and Malmö subcohorts of the prospective, population-based Osteoporotic Fractures in Men Study-Sweden (MrOS-Sweden) study were followed for a median of 12.2 years for all-cause mortality and 5.1 years for incident CVD and cancer. During follow-up, 338 participants developed incident CVD, and 249 developed cancer; 1,207 (67%) deaths occurred. Eligibility criteria were limited to men who could walk unaided, self-report information, and provide informed consent.

High levels of FT4, per one standard deviation (SD) increase, showed a significant association with increased all-cause mortality (hazard ratio [HR] 1.23] and incident CVD events (HR 1.25). No such association was noted for risk of cancer. Of note, the association between FT4 and CVD was driven mainly by cerebrovascular events (HR 1.56). Serum TSH showed no association with mortality, CVD, or cancer risk.

This study demonstrates an association between raised FT4, and higher mortality and cerebrovascular risk. Analyses were performed both in the overall cohort and specifically in men with normal serum TSH levels. Hence, it would be more prudent to monitor FT4 levels in older men rather than relying on TSH for cardiovascular risk stratification. The authors also state, "…if FT4 levels are measured early, preventive actions can be initialized to minimize the risk of mortality and CVD events".

Reference

1. Svensson J, et al. Higher serum free T4 is associated with increased risk of mortality and cerebrovascular events in elderly men. J Endocr Soc. 2025;9(9):bvaf121.

Mid-Afternoon may be the Best Time for Inhaler Use in Asthma

Mid-afternoon dosing of inhaled corticosteroid (ICS), between 3 and 4 PM, is most effective in decreasing nocturnal worsening of asthma, compared to morning or twice-daily dose, without increasing the steroid-associated morbidity. These findings from a UK study were published in the journal *Thorax*[1].

This randomized, three-way crossover trial was conducted to evaluate the impact of the time of dosing of ICS on lung function and biomarkers in patients with mild to moderate atopic asthma. Twenty-five participants were randomized to receive beclometasone dipropionate in one of the following three regimens for 28 days: single dose of 400 µg once daily in the morning (08:00-09:00, OD_{AM}), 400 µg once daily dose in the afternoon (15:00-16:00, OD_{PM}), or twice daily dose of 200 µg in the morning and evening (BD) (08:00-09:00 and 20:00 and 21:00). Each regimen had a 2-week washout period between phases. Spirometry readings and biomarker (blood eosinophils, serum cortisol) levels were measured every 6 hours over 24 hours after the run-in and post-treatment periods.

Twenty-one out of the 26 participants completed all treatment regimens. All the three regimens improved nocturnal lung function. However, the largest improvement in evening (measured at 22:00) lung function was seen with the OD_{PM} regimen (+160 mL) compared with OD_{AM} (-20 mL) and BD (+80 mL). OD_{PM} yielded superior suppression of nocturnal (22:00 and 04:00) blood eosinophil counts compared with the other two regimens. All three regimens improved overall asthma control, reduced fractional exhaled nitric oxide, and lowered serum cortisol, with no significant between-group differences.

Asthma symptoms usually worsen at night or in early morning. The present study illustrates that OD_{PM} dosing of ICS effectively improved nocturnal lung function and reduced inflammation than the other dosage timings investigated in the study. Therefore, prescribing treatment in accordance with the body's circadian rhythms enhances the efficacy of ICS and paves the way for personalized dosing schedules. Nonetheless, the authors note the need for further trials to confirm these findings and to determine which patients would benefit the most from chronotherapy.

Reference

1. Wang R, et al. The impact of dosage timing for inhaled corticosteroids in asthma: a randomised three-way crossover trial. Thorax. 2025;80(8):504-11.

Small Dense LDL-C: A Marker for Lower Extremity Arterial Disease in Type 2 Diabetes

Raised small dense low-density lipoprotein cholesterol (LDL-C) is significantly associated with lower extremity arterial disease in patients with type 2 diabetes, suggests a study published in the *Journal of Diabetes and its Complications*[1].

The aim of this cross-sectional study was to assess the predictive value of small dense LDL-C for lower extremity arterial disease in participants with type 2 diabetes, aged 18 to 70 years. Sixty-six individuals with type 2 diabetes and 120 with both type 2 diabetes and lower extremity arterial disease were selected for the study with 47 healthy individuals acting as the control group. The various metabolic parameters, such as fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), and apolipoprotein B (ApoB), were compared between the three groups. Those with type 2 diabetes and with both diabetes and lower extremity arterial diseases had higher prevalence of sedentary lifestyle habits and smoking versus the healthy controls.

Results showed significantly higher levels of small dense LDL-C in type 2 diabetes patients compared to controls (1.06 vs. 0.77 mmol/L); the levels were even higher in those who also had lower extremity arterial disease (1.33 mmol/L). A positive correlation was observed between small and dense LDL-C and FPG, HbA1c, C-peptide, triglycerides, LDL-C, ApoB, and body mass index (BMI). The predictive value was assessed using a receiver operating characteristic (ROC) curve. This analysis demonstrated a good predictive value of small dense LDL-C for lower extremity arterial disease with area under the curve (AUC) of 0.765. After adjusting for conventional risk factors, small dense LDL-C was determined to be an independent risk factor for LEAD with odds ratio (OR) of 7.88, along with fasting C-peptide, HbA1c ApoB, duration of diabetes, and sedentary lifestyle.

Small dense LDL-C has been demonstrated to be the most atherogenic lipoprotein parameter[2]. This study highlights small dense LDL-C as a stronger predictor of lower extremity arterial disease, which "outperforms conventional LDL-C in risk stratification", according to the authors. Hence, it may be a valuable biomarker for early detection of lower extremity arterial disease in this high-risk population and should be incorporated into routine evaluations.

References

1. Zheng D, et al. Elevated small dense low-density lipoprotein-cholesterol as a risk factor for lower extremity arterial disease in patients with type 2 diabetes mellitus. J Diabetes Complications. 2025;39(10):109136
2. Ikezaki H, et al. Small dense low-density lipoprotein cholesterol is the most atherogenic lipoprotein parameter in the prospective Framingham Offspring Study. J Am Heart Assoc. 2021;10(5):e019140.

Glycemic Variability and the Risk of Peripheral Neuropathy in Diabetes

Diabetes patients with increased glycemic variability are at a substantially higher risk of developing diabetic peripheral neuropathy (DPN), as per a study recently published in the journal *Diabetes Research and Clinical Practice*[1].

A systematic review and meta-analysis was conducted to identify any relationship between glycemic variability, as measured by continuous glucose monitoring (CGM), and the risk of developing DPN in patients with type 1 and type 2 diabetes. Nine studies with a total of 3,649 patients were included in the meta-analysis.

Analysis revealed a significant association between increased glycemic variability and the incidence of DPN as indicated by various glycemic variability metrics. Patients with higher SD in blood glucose levels are over twice as likely to develop DPN compared to those with lower SD with OR of 2.58. Increased mean amplitude of glycemic excursions was associated with a 90% higher risk of developing DPN (OR 1.90). Higher mean of daily difference was also strongly associated with nearly a threefold increase in the risk of DPN (OR 2.88). These findings underscore the potential of glycemic variability metrics as markers for the onset of DPN. Integrating these metrics into routine diabetes care could serve as an early warning system, allowing for more targeted interventions aimed at mitigating the risk of neuropathy.

Reference

1. Jia Y, et al. Diabetic peripheral neuropathy and glycemic variability assessed by continuous glucose monitoring: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2024;213:111757.

Benefits of Testosterone Replacement Therapy in Cirrhosis

In men with advanced liver disease, testosterone levels are usually reduced and decline further as the severity of liver disease worsens. Both conditions share clinical features such as anemia, sarcopenia, bone disease, and gynecomastia[1].

Testosterone replacement therapy reduces mortality and morbidity with lower risk of liver decompensation

events, particularly ascites and variceal bleeding, in older men with cirrhosis and hypogonadism, according to findings from a study published in *Clinical Gastroenterology and Hepatology*[2,3].

A target trial emulation was conducted to evaluate the impact of testosterone replacement therapy in men with newly diagnosed cirrhosis and hypogonadism. Medicare data from 2008 to 2020 was used for this purpose. The key clinical outcomes were death, decompensation events, fractures, and hepatocellular carcinoma. Out of the 3,799 patients, 282 (7.4%) received testosterone therapy, while 3,517 did not receive testosterone. The median ages ranged from 69 to 70 years in the two groups.

The mortality rates were significantly lower in men who received testosterone replacement therapy with subdistribution hazard ratio (sHR) of 0.92. Testosterone therapy was associated with reduced risk of decompensation events compared with nonusers (sHR 0.92), particularly ascites that necessitated paracentesis (sHR 0.83) and variceal bleeding (sHR 0.68). However, the rates of hepatic encephalopathy requiring hospitalization (sHR 0.92), fractures (sHR 0.99), or hepatocellular carcinoma (sHR, 1.09) did not differ significantly between testosterone users versus nonusers. There was considerable variation in treatment effects across baseline subgroups.

Hence, patients with cirrhosis should be screened for hypogonadism and prescribed testosterone as a potential therapeutic option if found deficient taking into consideration the potential benefits and risks.

References

1. Sinclair M, et al. Testosterone in men with advanced liver disease: abnormalities and implications. J Gastroenterol Hepatol. 2015 Feb;30(2):244-51.
2. Tapper EB, et al. Testosterone replacement reduces morbidity and mortality for most patients with cirrhosis. Clin Gastroenterol Hepatol. 2025 Mar 15:S1542-3565(25) 00200-9.
3. Saha R. In men with cirrhosis, testosterone Tx linked to lower morbidity and mortality. Dated May 7, 2025. Available at: https://www.gastroenterologyadvisor.com/news/in-men-with-cirrhosis-testosterone-tx-linked-to-lower-morbidity-and-mortality/. Accessed September 9, 2025.

Unmasking Cushing's Syndrome in Obesity

Selective screening of persons with metabolically unhealthy obesity for Cushing's syndrome is more likely to increase the probability of diagnosing Cushing syndrome, suggests a study from Turkey published August 9, 2024, in the *International Journal of Obesity*[1].

A team of endocrinologists from Turkey retrospectively analyzed data from 1,008 patients with obesity who underwent screening for Cushing's syndrome at an endocrinology outpatient clinic between December 2020 and June 2022. Their mean age was 40 years, and the majority were female (~83%). The median BMI was 43.7 kg/m². Based on the presence of comorbid conditions, 779 were categorized as metabolically unhealthy obesity (MUO); 23% had diabetes, 29% had prediabetes, ~25% had hypertension, and 78% had dyslipidemia; less than 5% had coronary artery disease. The remaining 229 had metabolically healthy obesity (MHO). The 1 mg overnight dexamethasone-suppression test (DST) was utilized to screen for Cushing's syndrome. A serum cortisol level < 1.8 μg/dL indicated normal suppression.

The cortisol levels following the 1 mg DST were significantly higher in those with MUO vis-a-vis MHO. About 1.2% (n = 12) patients within the entire study group had a cortisol level of ≥1.8 following the 1 mg DST. Eleven of the 12 patients with a cortisol level of ≥1.8 had MUO. This group also had higher FPG, HbA1c, triglyceride, and LDL-C levels and lower high-density lipoprotein cholesterol (HDL-C) levels. Hypercortisolism was definitively diagnosed in 2 patients with an ensuing overall prevalence of 0.2%. The specificity of the 1 mg DST in screening for Cushing's syndrome was 99%, while the sensitivity was 100%.

This study highlights two main findings. Firstly, it demonstrates the high specificity of the 1 mg DST as a screening test for Cushing's syndrome, including in patients with obesity. This has clinical relevance since there is considerable overlap of signs and symptoms between the two conditions. Secondly, it reaffirms the low prevalence of Cushing's syndrome in patients with obesity, which *per se* is a rare condition.

Hence, rather than screening all individuals with obesity, it would be more prudent to screen those with the MUO phenotype.

Reference

1. Hepsen S, et al. Cushing's syndrome screening with the 1-mg dexamethasone suppression test in metabolically healthy and unhealthy obesity phenotypes. Int J Obes (Lond). 2024;48(11):1620-4.

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