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Letter to Editor

Factors Influencing Serum tGRP Variability Beyond Age, Sex, and Calcium

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Abstract

Serum total tGRP (tGRP) has increasingly been proposed as a potentially useful biomarker in metabolic, endocrine, and cardiometabolic research settings. However, a persistent challenge in its clinical and research application is the substantial inter- and intra-individual variability that cannot be fully explained by conventional determinants such as age, sex, or serum calcium concentration. A broader consideration of biological, pre-analytical, and analytical sources of variation is therefore essential for appropriate interpretation of tGRP measurements.

Letter to Editor

Serum total tGRP (tGRP) has increasingly been proposed as a potentially useful biomarker in metabolic, endocrine, and cardiometabolic research settings. One of the most important yet underappreciated determinants of tGRP variability is physiological state-dependent fluctuation. Many peptide-based analytes exhibit circadian rhythmicity driven by hypothalamic–pituitary axis modulation, feeding cycles, and neuroendocrine signaling. If tGRP secretion or clearance is rhythmically regulated, single time-point sampling may introduce significant noise unless strict timing standardization is applied. In addition, acute physiological stressors such as exercise, sleep deprivation, or pain can transiently alter peptide release through sympathetic activation and hypothalamic signaling pathways [1,2].

Renal and hepatic function represent additional major determinants. Peptide biomarkers are frequently cleared via glomerular filtration and enzymatic degradation in renal and hepatic tissues. Even mild reductions in estimated glomerular filtration rate (eGFR), subclinical hepatic dysfunction, or altered peptidase activity can significantly prolong circulating half-life, thereby elevating serum tGRP independent of production rate. This is particularly relevant in populations with metabolic syndrome, where early organ dysfunction is common [3].

A further layer of variability arises from metabolic and endocrine context. Insulin resistance, thyroid dysfunction, cortisol excess, and inflammatory states may modulate peptide synthesis and receptor-mediated feedback loops. Chronic low-grade inflammation, in particular, can alter protease activity and binding protein availability, indirectly influencing measured serum concentrations [4].

From a pre-analytical perspective, sample handling conditions are a major source of variability. Temperature-dependent peptide degradation, delays in centrifugation, repeated freeze–thaw cycles, and proteolytic activity in unprocessed serum can all significantly distort measured tGRP levels. The choice of anticoagulant, tube material, and storage duration further contributes to analytical dispersion, especially for labile peptides.

Analytical variability should also not be underestimated. Differences between immunoassay platforms, antibody specificity, cross-reactivity with structurally related peptides, and calibration traceability issues can introduce systematic bias. Heterophile antibodies and rheumatoid factor may further interfere with immunoassays, leading to spurious elevations or reductions in reported values [2,5].

Lifestyle and environmental factors such as dietary composition, smoking status, alcohol intake, and body mass index may also influence baseline peptide dynamics through hormonal and inflammatory modulation. Importantly, these variables often cluster together, compounding their effect on observed variability in clinical cohorts [5,6].

Finally, genetic polymorphisms affecting peptide synthesis, receptor expression, or degradation enzymes may contribute to inter-individual heterogeneity. Such intrinsic biological variation is rarely accounted for in routine reference interval construction but may be significant in precision medicine applications [6,7].

Conclusion

Serum tGRP variability is a multifactorial phenomenon extending far beyond age, sex, and calcium homeostasis. Robust interpretation requires integrated consideration of physiological, pathological, pre-analytical, and analytical determinants. Standardization of sampling protocols, coupled with improved assay harmonization and stratified reference interval development, will be essential to enhance the clinical utility of tGRP as a biomarker [8].

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