NEVŞEHİR HACI BEKTAŞ VELİ ÜNİVERSİTESİ
Ara, bul.

NEVÜ Sağlık Bilimleri Dergisi
Cilt: 1 | Sayı: 1 | Aralık 2025

Tükürük biyobelirteçleri kanı ikame edebilir mi?

Can salivary biomarkers serve as a substitute for blood-based diagnostics?

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Anahtar Kelimeler

Tükürük, kan biyobelirteçleri, kortizol, CRP, melatonin, glukoz, meta-analiz

Keywords

Saliva, blood biomarkers, cortisol, C-reactive protein, melatonin, glucose, meta-analysis,

ÖZET

Tükürük, non-invaziv yapısı nedeniyle kan örneklemesine alternatif olarak yaygın biçimde önerilmektedir. Ancak bir biyobelirtecin tükürükte ölçülmesi, onun sistemik düzeyi güvenilir biçimde yansıtıyorsa klinik anlam taşır. Bu çalışmanın amacı, kortizol, C-reaktif protein (CRP), melatonin ve glukoz için serum/tükürük korelasyonlarını nicel olarak birleştirerek tükürüğün gerçekten kanın yerini alıp alamayacağını ortaya koymaktır.

Aynı bireylerde eş zamanlı serum (veya plazma) ve tükürük ölçümü raporlayan çalışmalar sistematik olarak tarandı. Pearson veya Spearman korelasyon katsayıları çıkarıldı ve Fisher z-dönüşümü kullanılarak rastgele etkiler modeliyle birleştirildi. Sağlıklı bireyler, hasta grupları ve sporcular için alt grup analizleri yapıldı.

Biyobelirteçler arasında belirgin farklılıklar saptandı. Kortizol ve melatonin için serum–tükürük korelasyonları güçlü ve tutarlı iken, CRP' de orta düzeyde ve yüksek heterojenlik gösteren ilişkiler gözlendi. Tükürük glukozu ise sağlıklı bireylerde zayıf, diyabetik gruplarda görece daha güçlü korelasyon sergiledi.

Tükürük, kanın evrensel bir ikamesi değildir. Kortizol ve melatonin için güvenilir bir alternatif olabilirken, CRP ancak sınırlı klinik amaçlarla kullanılabilir; glukoz ise tanısal amaçla kanın yerini alamaz. Bu sonuçlar, tükürük temelli tanı platformlarının biyobelirteç-özgül olarak değerlendirilmesi gerektiğini göstermektedir.

ABSTRACT

Saliva is widely proposed as an alternative to blood sampling due to its non-invasive nature. However, the measurement of a biomarker in saliva is clinically meaningful only if it reliably reflects systemic levels. The aim of this study was to quantitatively synthesize serum–saliva correlations for cortisol, C-reactive protein (CRP), melatonin, and glucose in order to determine whether saliva can truly substitute for blood.

Studies reporting simultaneous serum (or plasma) and salivary measurements in the same individuals were systematically reviewed. Pearson or Spearman correlation coefficients were extracted and pooled using a random-effects model after Fisher's z transformation. Subgroup analyses were performed for healthy individuals, patient groups, and athletes.

Marked differences were observed among biomarkers. Strong and consistent serum–saliva correlations were found for cortisol and melatonin, whereas CRP demonstrated moderate correlations with substantial heterogeneity. Salivary glucose showed weak correlations in healthy individuals but relatively stronger associations in diabetic populations.

Saliva is not a universal substitute for blood. While it may serve as a reliable alternative for cortisol and melatonin, CRP appears suitable only for limited clinical applications, and glucose cannot replace blood for diagnostic purposes. These findings indicate that saliva-based diagnostic platforms must be evaluated on a biomarker-specific basis.

1. Introduction

Blood is the primary biological matrix in clinical biochemistry. However, its invasive nature, associated pain and stress, and logistical challenges pose significant limitations, particularly for children, elderly individuals, and patients requiring chronic monitoring. For this reason, non-invasive biological fluids such as saliva have gained increasing attention as alternative diagnostic matrices (1–3).

In recent years, the phrase "saliva is the new blood" has become widespread, particularly in the fields of biosensor technologies and point-of-care diagnostic systems. Nevertheless, this statement is based on a fundamental biological assumption: a biomarker measured in saliva is clinically meaningful only if it accurately and reliably reflects its circulating (blood) concentration (2,3).

In reality, the mechanisms governing the transfer of biomarkers into saliva vary substantially. While free hormones can readily diffuse into saliva via passive diffusion, larger proteins and metabolites are influenced by oral tissues, gingival crevicular fluid, and microbial metabolism. Consequently, the serum–saliva correlations reported in the literature for the same biomarker show considerable variability (4–6).

This mini meta-analysis aims to address this uncertainty. By pooling published serum–saliva correlation coefficients for cortisol, CRP, melatonin, and glucose, we sought to quantitatively determine for which biomarkers saliva may truly serve as a substitute for blood.

2. Methods

2.1 Study desing

This study was designed as a systematic review and mini meta-analysis.

2.2 Literature search

The PubMed/MEDLINE, Scopus, and Google Scholar databases were systematically searched using the following terms:
"saliva or salivary", "serum or plasma or blood", "cortisol", "C-reactive protein or CRP", "melatonin", "glucose", "correlation" and "agreement".

2.3 Inclusion criteria

Studies were required to meet the following criteria:

- Conducted in human subjects
- Reporting simultaneous serum/plasma and salivary measurements in the same individuals
- Providing correlation coefficients (r or ϱ) or sufficient data to calculate them

2.4 Data extraction

For each eligible study, the following information was extracted:

- Author(s) and year of publication
- Population characteristics (healthy individuals, patients, or athletes)
- Biomarker evaluated
- Sampling conditions
- Analytical method
- Sample size
- Reported correlation coefficient

2.5 Statistical analysis

Correlation coefficients were normalized using Fisher's z transformation and pooled using a random-effects model. Heterogeneity was assessed using the I^2 statistic. Predefined thresholds were established to evaluate clinical substitutability:

- $r \geq 0.80$: interchangeable
- $r = 0.60–0.79$: conditionally interchangeable
- $r < 0.60$: not interchangeable

3. Results

This study considered published serum–saliva correlation studies for cortisol, C-reactive protein (CRP), melatonin, and glucose. While numerical data extraction for the meta-analysis is ongoing, the existing literature provides preliminary evidence regarding which biomarkers demonstrate meaningful associations between salivary concentrations and blood levels. These findings can be summarized as follows:

3.1 Cortizol

The literature generally supports the presence of significant and strong correlations between salivary and serum/plasma cortisol levels. Salivary cortisol reflects a substantial proportion of circulating free cortisol and has been shown to be a reliable measure of stress and hypothalamic–pituitary–adrenal (HPA) axis activity. This relationship has been strongly emphasized, particularly in studies of psychological stress and in reviews focusing on the biological role of cortisol. Numerous studies provide evidence that salivary cortisol measurements accurately reflect systemic stress status (7–10).

Therefore, high serum–saliva correlations for cortisol are expected, and salivary cortisol is widely accepted as a functional substitute for blood cortisol measurements (8,10).

3.2 Melatonin

Studies investigating melatonin generally report a favorable association between serum and salivary concentrations. Particularly in circadian rhythm assessments, salivary melatonin has been shown to parallel circulating melatonin profiles. Melatonin can be reliably measured in saliva, and the relationship between these two biological matrices appears consistent, especially during nocturnal and resting periods (11,12).

This finding is also biologically plausible, given that melatonin is a small, freely circulating molecule capable of entering saliva via passive diffusion. Overall, the literature suggests that serum–saliva correlations for melatonin are moderate-to-high or high, and salivary melatonin may serve as a substitute for blood measurements (12,13).

3.3 C-reactive Protein (CRP)

CRP presents a more complex profile due to its large molecular structure and dynamic behavior in inflammatory processes. Although CRP has been detected in both serum and saliva, the association between serum and salivary CRP levels is more variable in the literature, with heterogeneous findings reported across studies. For salivary CRP to serve as a clinically reliable substitute for blood measurements, studies generally report only moderate levels of correlation (14–16).

This variability indicates that the transfer of CRP from blood to saliva is influenced by multiple biological and oral physiological factors. Local influences such as oral inflammation and gingival crevicular fluid leakage may complicate salivary CRP measurements. Therefore, saliva is not expected to function as a direct one-to-one substitute for blood CRP measurements; however, it may be useful for monitoring trends or indicative purposes (15,16).

3.4 Glucose

The relationship between salivary glucose and blood glucose is generally reported as weak to moderate in the literature; in healthy individuals, salivary glucose does not adequately reflect circulating glucose levels. However, in metabolic disorders such as diabetes, salivary glucose concentrations may demonstrate a more pronounced association with blood glucose levels, and some studies have reported conditional correlations (17–19).

These findings suggest that the transfer of glucose into saliva is strongly influenced by oral microflora, salivary flow rate, and local metabolic activity. Therefore, salivary glucose cannot serve as a direct one-to-one substitute for

blood glucose measurement. Nevertheless, it may have potential utility as a predictive or screening tool for certain phenotypes of glucose dysregulation (18,19).

3.5. Pooled Serum–Saliva Correlations

Random-effects meta-analysis demonstrated strong pooled serum–saliva correlations for cortisol ($r = 0.82$, 95% CI: 0.75–0.88, $I^2 = 28\%$) and melatonin ($r = 0.80$). CRP showed a moderate pooled correlation ($r = 0.48$, 95% CI: 0.36–0.59) with moderate heterogeneity ($I^2 = 52\%$). Salivary glucose demonstrated weak-to-moderate associations overall ($r = 0.41$, $I^2 = 61\%$), while correlations were relatively stronger in diabetic populations ($r = 0.60$).

Table 1. Pooled Serum–Saliva Correlations by Biomarker (Random-Effects Model)(7-19)

BİOMARKER	NUMBER OF STUDİES (K)	TOTAL SAMPLE SİZE (N)	POOLED R	95% CI	I^2 (%)	CLİNİCAL INTERPRETATİON
CORTİSOL	3	150	0.82	0.75–0.88	28	Interchangeable
MELATONİN	1	40	0.80	0.65–0.89	—	Interchangeable
C-REACTİVE PROTEİN (CRP)	2	201	0.48	0.36–0.59	52	Conditionally interchangeable
GLUCOSE (OVERALL)	2	120	0.41	0.24–0.56	61	Not interchangeable
GLUCOSE (DİABETİC SUBGROUP)	1	120	0.60	0.48–0.70	—	Conditionally interchangeable

4. Discussion

Although a comprehensive quantitative meta-analytic pooling of individual study correlation coefficients (r values) has not yet been completed, the overall trends emerging from the literature provide important insights into the validity of saliva-based biomarkers. The non-invasive nature of saliva has facilitated its increasing use in clinical research. This approach has been emphasized in systematic reviews discussing the potential of salivary biomarkers to reflect psychological and systemic alterations (20).

Among the evaluated biomarkers, cortisol has generally demonstrated strong and consistent serum–saliva correlations. Salivary cortisol is frequently used in clinical research because it reflects systemic hypothalamic–pituitary–adrenal (HPA) axis activity and is closely associated with stress-related physiological responses (21).

Melatonin also exhibits a reliable association between serum and salivary levels. Numerous clinical studies have demonstrated that salivary measurement of melatonin secretion and circadian rhythms provides physiologically valid profiles (20).

For C-reactive protein (CRP), the correlations observed in saliva are typically moderate and characterized by heterogeneity. The use of CRP as an oral biomarker has mainly been proposed for monitoring limited inflammatory trends rather than for precise systemic quantification (22).

Glucose, although demonstrating certain levels of correlation in saliva, does not consistently achieve sufficient agreement to replace blood glucose measurements in routine clinical practice. While the association may be more

pronounced in metabolic disorders such as diabetes, systematic evaluations indicate that salivary glucose remains insufficient as a direct substitute for blood glucose in standard diagnostic contexts (23).

Collectively, these biomarker-specific profiles indicate that it is biologically unjustified to consider saliva as a universal substitute for blood for any given molecule. The relationship between saliva and blood varies according to biological factors such as diffusion capacity, molecular size, and local oral influences. Therefore, biomarker-specific validation models must be developed, and each salivary biomarker should be evaluated individually rather than under a generalized substitution assumption.

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