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The Link Between Salivary Amylase Activity, Overweight, and Glucose Homeostasis

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Abbreviations used in the Thesis

AMY1	Amylase, alpha 1 gene
BMI	Body Mass Index
FFA	Free fatty acid
GDF-15	Growth differentiation factor-15
GLP-1	Glucagon-like peptide-1
HDL-C	High-density lipoprotein cholesterol
HOMA2-%B	Homeostatic model assessment 2 of beta-cell function
HOMA2-%S	Homeostatic model assessment 2 of insulin sensitivity percentage
HOMA2-IR	Homeostatic model assessment 2 of insulin resistance
HSA-CR	High-salivary-amylase calorie restriction group
HSA-LS	High-salivary-amylase low-starch group
IKKβ	Iκb kinase beta
IR	Insulin resistance
IRS	Insulin receptor substrate
LDL-C	Low-density lipoprotein cholesterol
LSA-CR	Low-salivary-amylase calorie restriction group
LSA-LS	Low-salivary-amylase low-starch group
mTORC1	Mechanistic target of rapamycin
RNA	Ribonucleic acid
SAA	Salivary amylase activity
SREBP-1c	Sterol Regulatory Element-Binding Protein 1c
T0	Baseline
T1	30 minutes after starch-containing muesli consumption
TyG	Triglyceride-glucose index
VF	Visceral fat

Introduction

The growing global burden of overweight and obesity has led to a surge in metabolic disorders, including insulin resistance, type 2 diabetes, and cardiovascular disease. Although the pathogenesis of these conditions is multifactorial, increasing attention is being paid to early, non-invasive biomarkers that can identify individuals at risk and offer insights into underlying physiological mechanisms (Al Akl et al., 2022; Habobe et al.2025).

Salivary amylase activity (SAA), which catalyses the initial hydrolysis of α-1,4-glycosidic linkages in dietary starches, has traditionally been regarded as a digestive enzyme (Freitas et al 2017). However, accumulating evidence indicates that SAA has functions extending beyond starch digestion, potentially contributing to the regulation of glucose homeostasis, insulin secretion, and overall energy balance (Mandel et al., 2010; Mejía-Benítez et al., 2015). Recent studies further demonstrate that interindividual variations in SAA are associated with differences in postprandial glycaemic responses, insulin dynamics, and adiposity distribution (Mandel & Breslin, 2012; Sekine et al., 2024). Collectively, these findings suggest that SAA may serve as a proxy for broader neuroendocrine and metabolic regulatory pathways involved in energy homeostasis.

Visceral adiposity, a hallmark of metabolically unhealthy overweight, is strongly associated with insulin resistance and systemic inflammation (Er et al., 2016; Tsuchiya et al., 2025). Identifying upstream markers that correlate with visceral fat accumulation and impaired glucose metabolism is critical for developing preventive strategies. Several observational studies have suggested that individuals with lower SAA levels may be predisposed to greater visceral fat accumulation and blunted cephalic-phase insulin responses, although the mechanisms remain poorly understood (Al-Akl et al., 2022; Marquina et al., 2019).

Aim of the Thesis

This Thesis builds upon these hypotheses and aims to clarify the associations between SAA, overweight status, and glucose homeostasis. Unlike previous work focused on isolated aspects, this study takes an integrative approach using data from a single population cohort, examined through multiple analytical approaches. The results are presented across three published articles, each emphasising different dimensions of the metabolic network involving SAA.

Objectives of the Thesis

1 Conduct a comprehensive review of current scientific literature to elucidate the physiological role of salivary amylase activity (SAA) and its potential associations with metabolic health, focusing on its impact on glucose regulation, insulin response, and adipose tissue distribution.

2 Investigate the relationships between salivary amylase activity, visceral fat accumulation, and surrogate markers of insulin resistance, such as the triglyceride-glucose (TyG) index.
3 Conduct a physician-guided observational design with a cross-sectional analysis component to evaluate the impact of dietary interventions on metabolic markers in a well-defined cohort of overweight women with varying salivary amylase activity (SAA) of reproductive age to evaluate differences in anthropometric and metabolic parameters in response to a 12-week low-starch and calorie-restriction diet intervention.

Study Markers and Parameters

1 Anthropometric Markers:
   - Body Mass Index (BMI)
   - Visceral Fat Percentage (VF %)
2 Carbohydrate metabolism Markers:
   - Glucose
   - C-peptide
   - Active GLP-1
   - Glucagon
3 Insulin Sensitivity and Resistance Markers:
   - HOMA2-%S (Insulin Sensitivity)
   - HOMA2-IR (Insulin Resistance)
   - HOMA2-%B (Beta-cell Function)
   - TyG- Triglyceride-Glucose
4 Lipid profile:
   - Total Cholesterol
   - Low-Density Lipoprotein (LDL
   - High-Density Lipoprotein (HDL)
5 Circulating gut/metabolic markers:
   - GDF15
   - Leptin
   - Butyrate

Hypotheses of the Thesis

1 Salivary amylase activity (SAA) is inversely associated with visceral adiposity and may serve as a non-invasive biomarker for early metabolic dysregulation in overweight individuals.

2 SAA's role in maintaining glucose homeostasis is mediated indirectly through mechanisms such as visceral fat modulation, rather than exerting a direct effect on systemic glucose handling
3 The effect of low-starch and calorie-restriction diet on metabolic parameters differs according to the level of salivary amylase activity (SAA).

Novelty of the Thesis

This Thesis introduces an innovative perspective by exploring salivary amylase activity (SAA) as a potential upstream modulator of metabolic health in overweight women of reproductive age. While previous research has primarily focused on SAA's role in digestive physiology and acute postprandial responses, this work extends its significance to chronic metabolic adaptations. Specifically, it examines the relationships between SAA, visceral adipose tissue distribution, and markers of glucose homeostasis.

Key contributions of the Thesis include:

1 Inverse Association Between SAA and Visceral Fat: The study demonstrates a significant inverse relationship between SAA and visceral fat percentage, independent of total body fat mass. This finding aligns with evidence from the research, which highlights that higher SAA activity is associated with reduced visceral fat accumulation, a critical marker of metabolic risk. Mediation analysis further reveals that visceral fat mediates the relationship between SAA and the triglyceride-glucose (TyG) index, accounting for 45 % of the total effect. This positions SAA as a potential surrogate marker for metabolically unhealthy fat distribution.
2 Challenging the Direct Link Between SAA and TyG Index: Contrary to the assumption of a direct linear relationship between SAA and insulin resistance markers like the TyG index, the Thesis provides empirical evidence of their dissociation. The findings suggest that SAA's influence on metabolic health is primarily mediated through its impact on visceral fat, rather than directly affecting the TyG index. This challenges traditional views and calls for a deeper exploration of alternative regulatory pathways.
3 Salivary Diagnostics as a Non-Invasive Screening Tool: The research highlights the potential of salivary diagnostics as a cost-effective and non-invasive method for metabolic screening. By measuring SAA, it may be possible to identify individuals at risk for visceral obesity and insulin resistance early, enabling timely interventions.

4 Collectively, the Thesis proposes a paradigm shift from traditional glucose-centric models to a more integrative approach that emphasises the role of digestive-metabolic interactions. By leveraging salivary biomarkers, particularly SAA, this work contributes to refining the evaluation of metabolic health dynamics and underscores the importance of personalised nutrition strategies tailored to individual metabolic profiles.

Discussion

1 Overview of Key Findings

This study provides novel insights into the role of salivary amylase activity (SAA) as a potential biomarker for metabolic health in overweight women of reproductive age. The findings revealed significant associations between SAA, visceral fat percentage (VF %), and glucose homeostasis, highlighting the importance of SAA in modulating metabolic outcomes. Specifically, higher SAA was associated with lower VF %, suggesting a protective role against visceral fat accumulation. Furthermore, mediation analysis demonstrated that VF % partially mediates the relationship between SAA and the triglyceride-glucose (TyG) index, accounting for 45 % of the total effect.

The study also showed that tailored dietary interventions based on SAA levels, calorie restriction (CR) for high SAA individuals, and low-starch (LS) diets for low SAA individuals resulted in significant improvements in metabolic markers. These findings underscore the importance of personalised nutrition strategies in addressing metabolic health challenges, particularly in populations at risk for obesity-related disorders.

2 Impact on Glucose Homeostasis

The study highlights the differential effects of dietary interventions on glucose homeostasis based on salivary amylase activity:

- High Salivary Amylase Activity (HSA): Participants with HSA showed superior improvements in insulin sensitivity when following calorie-restricted diets. This suggests that individuals with higher enzymatic activity may benefit more from interventions targeting overall caloric intake reduction.
- Low Salivary Amylase Activity (LSA): Participants with LSA exhibited better glycaemic control on low-starch diets. This is likely due to reduced post-prandial glucose spikes and hyperinsulinemia, which collectively contribute to improved glucose regulation.

These findings pave the way for future research to further explore the mechanistic pathways underlying these associations and to validate the use of SAA as a biomarker in diverse populations. While the study reported associations between salivary amylase activity, overweight, and glucose homeostasis, the evidence does not establish direct causality.

3 Assessment of Post-Prandial Metabolic Biomarker Modulation Induced by Starch-Containing Muesli

The study provided detailed insights into the acute changes in active GLP-1 and leptin levels following the consumption of starch-containing muesli (T1) in individuals with high salivary amylase activity (HSA) and low salivary amylase activity (LSA). These changes highlight the role of enzymatic variability in modulating post-prandial metabolic responses.

The acute changes in active GLP-1 and leptin levels from T0 to T1 demonstrate the influence of salivary amylase activity on post-prandial metabolic responses.

Elevated salivary amylase activity facilitates rapid starch degradation and glucose absorption, potentially increasing GLP-1 release and enhancing metabolic outcomes.

HSA individuals exhibited quicker but less sustained increases in these markers, while LSA individuals showed slower but more prolonged elevations, potentially enhancing satiety and glycaemic control. These findings underscore the importance of tailoring dietary interventions based on enzymatic activity to optimise metabolic outcomes

4 Role of Salivary Amylase Activity in Metabolic Health

Salivary amylase activity (SAA) has emerged as a potential upstream modulator of metabolic health, influencing key processes such as visceral fat distribution and glucose-insulin homeostasis. This study demonstrated significant associations between SAA and visceral fat percentage (VF %), with higher SAA linked to lower VF %. This finding aligns with the hypothesis that individuals with elevated SAA activity may exhibit enhanced carbohydrate metabolism efficiency, which reduces postprandial glycaemic spikes and insulin demand, thereby mitigating lipogenesis and visceral fat accumulation.

The mediating role of VF % in the relationship between SAA and the triglyceride-glucose (TyG) index further underscores the metabolic significance of SAA. Mediation analysis revealed that VF % accounted for 45 % of the total effect of SAA on the TyG index, highlighting its critical role in linking digestive enzyme activity to markers of insulin resistance. This finding suggests that SAA may indirectly influence glucose-insulin homeostasis by modulating visceral fat distribution, a key determinant of metabolic health.

The study also explored the differential impact of dietary interventions tailored to SAA levels. Participants with high SAA activity responded more favourably to calorie-restricted diets, which were associated with reductions in VF % and improvements in insulin sensitivity. Conversely, participants with low SAA activity benefited more from low-starch diets, which improved glycaemic control and increased GLP-1 levels. These results emphasise the importance of personalised nutrition strategies that account for individual enzymatic

profiles, as SAA appears to play a pivotal role in determining the metabolic response to dietary composition.

Beyond its direct metabolic effects, SAA may also influence gut microbiota composition and short-chain fatty acid production, such as butyrate, which are known to impact glucose metabolism and insulin sensitivity. Although this study did not include direct microbiome profiling, the study highlights that salivary amylase activity influences butyrate production, with low-starch diets significantly increasing butyrate levels in women with low salivary amylase activity, thereby enhancing insulin sensitivity and supporting metabolic health, future research should investigate the interplay between salivary amylase activity, gut microbiota, and metabolic health.

5 SAA and Visceral Adiposity

The inverse association between salivary α-amylase activity (SAA) and visceral adiposity observed in our study aligns with previous evidence suggesting that individuals with higher SAA exhibit more favourable body fat distribution profiles (Al-Akl et al., 2022; Bonnefond et al., 2017). SAA plays a critical role in the initiation of starch digestion, hydrolysing α-1,4-glycosidic linkages in dietary polysaccharides to release maltose and maltotriose, thereby facilitating rapid glucose availability during the early postprandial phase (Mandel et al., 2010; Butterworth et al., 2011; Komeine et al., 2013).

Higher SAA levels have been associated with more efficient carbohydrate digestion, improved early-phase glycaemic control, and a more rapid onset of postprandial satiety, which may collectively contribute to reduced total energy intake and lower risk of excessive adiposity (Foster-Powell et al., 2002; Mandel & Breslin, 2012). From a mechanistic perspective, efficient pre-digestive starch hydrolysis may attenuate postprandial glycaemic excursions and insulin demand, thereby reducing chronic hyperinsulinemia, a major driver of de novo lipogenesis and visceral fat deposition (Jenkinset al., 1981; Elder, et al., 2018).

Chronic hyperinsulinemia activates the PI3K–Akt–mTORC1–SREBP-1c signalling axis, enhancing the transcription of lipogenic enzymes such as acetyl-CoA carboxylase and fatty acid synthase, ultimately promoting triglyceride synthesis and storage in visceral adipocytes (Porstmann et al., 2008; Kwon et al., 2020; Nakagawa et al., 2025).

6 Visceral Fat and the TyG Index

The observed strong positive correlation between visceral adiposity and the triglyceride–glucose (TyG) index in our cohort aligns with previous findings, which identify central fat accumulation as a key determinant of insulin resistance and metabolic syndrome (Simental-Mendía et al., 2008; Guerrero-Romero et al., 2010).Visceral adipose tissue (VAT) is

highly metabolically active and functions as an endocrine organ, secreting free fatty acids (FFAs), proinflammatory cytokines, and adipokines. These secretions collectively impair insulin signalling and disrupt glucose homeostasis (Wajchenberg, 2000).The TyG index, which primarily reflects hepatic insulin resistance, has been validated as a reliable surrogate marker for assessing insulin resistance (Guerrero-Romero et al., 2010).

Our findings propose a mechanistic framework in which salivary amylase activity (SAA) impacts metabolic health indirectly, not by directly regulating glucose or triglyceride metabolism, but by influencing fat distribution – specifically promoting the accumulation of visceral adipose tissue. The expansion of VAT contributes to insulin resistance through several interconnected molecular mechanisms.

Firstly, increased FFA flux from visceral fat depots to the liver elevates intracellular diacylglycerol (DAG) concentrations, which activates protein kinase C epsilon (PKCε). This activation inhibits insulin receptor substrate (IRS)-dependent signalling pathways, thereby impairing insulin action (Shulman et al., 2000; Janssen et al., 2025).Secondly, the remodeling of visceral adipose tissue is associated with macrophage polarisation toward a proinflammatory M1 phenotype. This process leads to elevated secretion of proinflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1).These factors activate c-Jun N-terminal kinase (JNK) and IκB kinase β (IKKβ) signalling pathways, further exacerbating insulin resistance (Hotamisligil et al., 2006; Lumeng et al., 2007; Guria et al., 2023).Thirdly, altered secretion of adipokines, including reduced levels of adiponectin and increased levels of resisting and retinol-binding protein 4 (RBP4), further impairs systemic insulin sensitivity and contributes to metabolic inflexibility (Kadowaki et al., 2006; Rabiee et al., 2025).

These mechanisms collectively outline a plausible biological pathway through which elevated SAA may exert protective effects on metabolic health. By enhancing oral starch hydrolysis and reducing postprandial glucose excursions, higher SAA levels may mitigate compensatory hyperinsulinemia, thereby limiting hepatic lipogenesis and the subsequent accumulation of metabolically harmful visceral fat. Supporting this integrative model, our mediation analysis revealed that approximately 45 % of the relationship between SAA and the TyG index is mediated through visceral fat volume. This finding highlights a potential indirect pathway that connects oral carbohydrate metabolism to systemic insulin sensitivity. It suggests that individual variability in SAA may represent broader adaptive mechanisms linking dietary starch processing to adipose tissue distribution and metabolic risk.

7 Lack of Direct Association Between SAA and TyG

While previous studies have proposed a direct link between SAA and glucose regulation (Perry et al., 2016; Mandel & Breslin, 2012), the present Thesis provides evidence supporting an indirect association. Although visceral fat demonstrated a moderate positive correlation with the TyG index ($r = 0.36$, $p < 0.01$), SAA did not correlate directly with TyG ($r = -0.12$, $p = 0.19$). This dissociation was further clarified through mediation analysis, which revealed that the effect of SAA on TyG was mediated by visceral adiposity (indirect effect $\beta = -0.09$, 95 % CI: −0.16 to −0.03, $p = 0.004$).

This observation suggests that the link between SAA and insulin resistance is more nuanced and may be mediated by intermediate variables such as visceral adiposity. This lack of a direct association contrasts with some studies reporting that higher SAA is predictive of better glycaemic control and lower insulin resistance.

8 Targeting Visceral Adiposity: Implications for Prevention

Specifically, the finding that 45 % of the total effect of SAA on the TyG index is mediated by VF highlights the biological plausibility of SAA acting as an upstream determinant of adiposity-driven metabolic dysfunction.

From a physiological standpoint, VF represents a unique metabolic compartment with distinct endocrine and inflammatory properties, contributing disproportionately to the development of IR and cardiometabolic disease (Gugliucci et al., 2022; Finelli et al 2013; Adeva-Andany et al 2024). Adipocytes in the visceral depot exhibit enhanced sensitivity to lipolytic stimuli and reduced responsiveness to insulin-mediated suppression of lipolysis, resulting in greater free fatty acid flux into the portal circulation and promotion of hepatic insulin resistance (Lundgren et al .2008; Zhao et al 2020). Adipocytes secrete pro-inflammatory adipokines, while macrophages infiltrating hypertrophic adipose tissue produce elevated levels of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines contribute to systemic inflammation and disrupt insulin signalling by interfering with insulin receptor substrate phosphorylation and downstream signalling cascades (Ali et al., 2020; Simons et al 2007; Weisberg et al., 2003). Consequently, interventions aimed at reducing VF mass hold significant potential for improving insulin sensitivity and mitigating metabolic risk.

The inverse association between SAA and VF suggests that individuals with higher enzymatic capacity for starch hydrolysis may experience a more favourable metabolic profile, potentially due to reduced postprandial insulin responses. (Choi et al., 2015). Therefore, SAA may exert indirect regulatory effects on adipose tissue distribution through its influence on

early-phase carbohydrate digestion and subsequent hormonal responses, particularly insulin dynamics.

These findings carry important implications for metabolic health strategies, particularly in the context of personalised nutrition and risk stratification. If SAA activity modulates visceral fat (VF) deposition via postprandial metabolic pathways, then enhancing SAA activity, either through dietary modulation or by targeting individuals with favourable AMY1 gene copy number profiles, could serve as a preventive strategy to reduce VF accumulation. Thus, SAA may represent not only a biomarker of metabolic risk but also a modifiable factor in interventions designed to prevent or reverse visceral adiposity and its associated complications.

9 Salivary Amylase Activity and Butyrate Production

The study demonstrated a weak but statistically significant correlation ($\rho = 0.0486$, $p < 0.05$) between salivary amylase activity and butyrate levels, suggesting that individuals with higher salivary amylase activity may exhibit enhanced starch digestion, leading to increased butyrate production. This aligns with previous research indicating that salivary amylase activity influences the availability of substrates for microbial fermentation in the gut, favouring the proliferation of butyrate-producing bacteria such as *Faecalibacterium prausnitzii* and *Roseburia spp*. (Flint et al., 2012; Khalil et al., 2024). Notably, women with high salivary amylase activity had significantly higher baseline butyrate levels compared to those with low activity (Mann-Whitney $U = 44$, $p < 0.05$). These findings suggest that salivary amylase activity plays a critical role in shaping gut microbiota composition and metabolic outcomes.

10 Rationale for Using Both HOMA2-IR and TyG Index

Insulin resistance is a multifaceted condition influenced by various metabolic pathways, including glucose regulation, lipid metabolism, and visceral adiposity. In this study, both the Homeostasis Model Assessment of Insulin Resistance 2 (HOMA2-IR) and the triglyceride-glucose (TyG) index were utilised to provide a comprehensive evaluation of insulin resistance and its relationship with salivary amylase activity (SAA) and dietary interventions. The inclusion of both markers was driven by their complementary strengths and their ability to capture distinct aspects of insulin resistance. The TyG index and HOMA2-IR represent two different approaches to assessing insulin resistance:

10.1 TyG Index

The TyG index, calculated using fasting triglyceride and glucose levels, is a reliable surrogate marker for insulin resistance, particularly in the context of lipid metabolism and visceral adiposity. It has been shown to correlate strongly with visceral fat, which is a central

focus of this study. The TyG index is less influenced by short-term fluctuations in insulin levels, making it a stable and practical marker for large-scale studies.

10.2 HOMA2-IR

HOMA2-IR is derived from fasting glucose and c-peptide levels, provides a direct measure of pancreatic beta-cell function and hepatic insulin sensitivity. It offers insights into the dynamics of insulin secretion and glucose regulation, which are critical for understanding the broader metabolic implications of SAA.

By incorporating both markers, the study was able to capture a more holistic view of insulin resistance, addressing both lipid-related and insulin-related pathways. The use of both markers allowed for cross-validation of the study's findings. Consistent trends observed across TyG index and HOMA2-IR strengthen the reliability of the results, while any discrepancies between the two markers provide valuable insights into the differential mechanisms of insulin resistance. For example, the TyG index may better reflect the lipid-related effects of SAA on visceral fat and triglyceride metabolism, while HOMA2-IR may capture the insulin secretion and hepatic glucose regulation pathways influenced by SAA.

The dual use of TyG index and HOMA2-IR enabled the study to explore the complex interactions between SAA, visceral adiposity, and glucose homeostasis. The findings suggest that SAA may influence glucose regulation through indirect mechanisms, such as gut-brain signalling, insulin secretion dynamics, or differential postprandial glycaemic responses. While the TyG index provided insights into the lipid-related pathways, HOMA2-IR offered additional information on the role of SAA insulin secretion and hepatic glucose regulation. The inclusion of HOMA2-IR ensures that the results are aligned with previous studies on insulin resistance, while the TyG index provides a novel perspective on the role of lipid metabolism in the context of SAA and visceral adiposity.

While the inclusion of both markers enhances the robustness of the study, certain limitations must be acknowledged:

The inclusion of both HOMA2-IR and TyG indexes in this study was essential for providing a comprehensive assessment of insulin resistance and exploring the metabolic role of salivary amylase activity. By leveraging the complementary strengths of these markers, the study was able to capture both lipid-related and insulin-related pathways, offering deeper insights into the complex mechanisms underlying glucose homeostasis and metabolic health. Future research should continue to explore the interplay between these markers to refine our understanding of insulin resistance and its relationship with SAA and dietary interventions.

11 Hormonal Influence and Study Population

The focus on women of reproductive age adds a unique dimension to the study, as hormonal fluctuations during the menstrual cycle can influence gut microbiota composition and butyrate production. Oestrogen, which is elevated during the follicular phase, has been shown to promote the growth of beneficial gut bacteria associated with butyrate production. Conversely, progesterone, which dominates the luteal phase, may attenuate these effects. While the study controlled for hormonal variability by measuring butyrate levels during the follicular phase, future research should explore the dynamic interactions between hormonal fluctuations, gut microbiota, and metabolic outcomes.

12 Personalised Nutrition Based on Salivary Amylase Activity (SAA)

This study highlights the potential of salivary amylase activity (SAA) as a biomarker for personalised nutrition strategies aimed at optimising metabolic health. Variability in SAA levels among individuals has been shown to influence dietary responses, particularly in relation to visceral fat accumulation, insulin sensitivity, and glucose homeostasis.

The findings from this study demonstrated that tailored dietary interventions based on SAA levels can significantly improve metabolic markers. Participants with high SAA activity (HSA) responded more favourably to calorie-restricted diets, which were associated with reductions in visceral fat percentage and enhanced insulin sensitivity. Conversely, participants with low SAA activity (LSA) benefited more from low-starch diets, which improved glycaemic control and increased GLP-1 levels, a key incretin hormone involved in glucose regulation.

Mechanistically, SAA influences the rate of starch digestion and glucose absorption, which in turn affects insulin dynamics and adipose tissue metabolism. Elevated SAA activity facilitates rapid starch hydrolysis, leading to improved glycaemic control and reduced insulin demand, which may attenuate lipogenesis and visceral fat accumulation. On the other hand, reduced SAA activity results in slower starch digestion, altered glycaemic responses, and potentially diminished GLP-1 secretion, which may impact satiety and glucose regulation.

The integration of SAA as a biomarker in personalised nutrition strategies offers several advantages. First, it provides a non-invasive and cost-effective method for assessing individual metabolic profiles. Second, it enables the development of tailored dietary recommendations that optimise metabolic outcomes based on enzymatic activity. For example, individuals with high SAA activity may benefit from calorie-restricted diets to reduce visceral fat, while those with low SAA activity may achieve better glycaemic control through low-starch diets.

These findings emphasise the need for further research to validate the use of SAA as a biomarker in diverse populations and to explore its long-term implications for metabolic health. Future studies should investigate the molecular mechanisms underlying the relationship

between SAA, gut microbiota composition, and metabolic outcomes, as well as the potential for dietary interventions to modulate SAA activity.

Personalised nutrition strategies based on SAA represent a promising approach to improving metabolic health and preventing obesity-related disorders. By leveraging salivary diagnostics and tailored dietary interventions, this research contributes to the growing field of precision nutrition and highlights the importance of integrating individual enzymatic profiles into dietary planning

13 Important Parameters That Did Not Change and Their Implications

In this study, total cholesterol, body weight, and growth differentiation factor-15 (GDF-15) remained unchanged following dietary intervention. Understanding the physiological and methodological factors underlying this stability is important for the interpretation of metabolic outcomes.

13.1 Total Cholesterol, LDL-C, and HDL-C

The stability of cholesterol parameters across intervention groups suggests that short-term modulation of carbohydrate intake has limited influence on plasma cholesterol homeostasis. Cholesterol levels are predominantly regulated by long-term dietary patterns, hepatic synthesis, and genetic determinants, making them less responsive to transient nutritional changes (Lecerf JM et al., 2011).

As the intervention primarily targeted carbohydrate restriction rather than fat composition, hepatic regulatory mechanisms, including cholesterol synthesis and LDL receptor activity, likely maintained circulating total cholesterol, LDL-C, and HDL-C within a stable range. This aligns with the observation that the intervention predominantly affected triglyceride levels, as reflected by changes in the TyG index, rather than total cholesterol fractions.

Furthermore, the relatively short intervention duration may have been insufficient for measurable alterations in cholesterol metabolism, which typically requires prolonged dietary exposure. Effective lipid modulation generally depends on the inclusion of cholesterol-lowering nutrients, such as soluble fibre, plant sterols, omega-3 fatty acids, and monounsaturated fats, which were not a focus of the current dietary design. The absence of these components likely contributed to the unaltered lipid profile despite improvements in other metabolic markers.

13.2 Body Weight

Reductions in visceral adiposity can occur independently of total weight loss, particularly when interventions enhance metabolic flexibility, insulin sensitivity, or mitochondrial efficiency (Holloszy JO et al., 2011). Redistribution of adipose tissue or modest

increases in lean mass may offset reductions in fat mass, resulting in stable total body weight. The moderate caloric restriction and relatively short duration likely further limited measurable changes. These findings underscore the limitations of body weight as an isolated marker of metabolic improvement and highlight the importance of body composition assessment, including visceral and subcutaneous fat indices.

13.3 Growth Differentiation Factor-15 (GDF-15)

GDF-15 is a stress-responsive cytokine associated with mitochondrial homeostasis and inflammatory regulation. Elevated concentrations are typically observed in states of oxidative stress, mitochondrial dysfunction, or systemic inflammation. The absence of significant change may reflect the participants relatively preserved metabolic health and the moderate intensity of the intervention, which likely did not elicit a sufficient mitochondrial or inflammatory response to alter GDF-15 expression (Tsai VWW et al., 2018). These results suggest that GDF-15 is more indicative of chronic metabolic stress than short-term dietary modulation

In this study, several metabolic and biochemical parameters, including total cholesterol, body weight, and growth differentiation factor-15 (GDF-15), did not demonstrate significant alterations following dietary interventions. Understanding the biological and methodological factors underlying this stability is essential for accurate interpretation of the results and for refining future experimental designs. The following sections discuss potential explanations for the lack of change and their broader implications.

14. Clinical and Translational Implications

The identification of non-invasive biomarkers for early detection of metabolic dysregulation is of great clinical importance, particularly in young women of reproductive age, in whom prevention of future metabolic disease is critical. Given that SAA can be easily measured in saliva and is responsive to both genetic and environmental factors, it may serve as a valuable tool for risk stratification, lifestyle intervention targeting, and personalised nutrition strategies (Perry et al., 2016; Carpenter et al., 2013). Additionally, since SAA is partially regulated by adrenergic activity, it may also serve as a surrogate marker of sympathetic nervous system (SNS) function. However, further longitudinal studies are required to establish causality and assess whether modulating SAA through dietary or behavioural means can influence metabolic trajectories.

15 Strengths and Limitations

This study has several **notable strengths** that contribute to its scientific rigor and the relevance of its findings:

1 Innovative Focus on Salivary Amylase Activity: The study provides a novel perspective by investigating salivary amylase activity (SAA) as a potential upstream modulator of metabolic health. While previous research has primarily focused on SAA in the context of digestive physiology, this study extends its relevance to chronic metabolic adaptations, highlighting its association with visceral fat distribution and glucose-insulin homeostasis.

2 Tailored Dietary Interventions: The study design incorporated personalised dietary strategies based on SAA levels, such as low-starch diets for individuals with low SAA and calorie-restricted diets for those with high SAA. This approach allowed for the exploration of individualised nutrition interventions and their impact on metabolic health.

3 Robust Statistical Analysis: The study employed appropriate statistical methods, including non-parametric tests, multivariable linear regression, and structural equation modelling (SEM) for mediation analysis. Adjustments for potential confounders such as age, BMI, physical activity, and dietary intake enhanced the reliability of the findings. The use of bootstrapping for mediation analysis further strengthened the robustness of the results.

4 Focus on Visceral Fat as a Mediator: The study highlighted the mediating role of visceral fat percentage in the relationship between SAA and the TyG index, providing valuable insights into the mechanisms underlying metabolic health. This approach advances the understanding of how visceral fat distribution contributes to glucose-insulin homeostasis.

5 Non-Invasive Biomarker Assessment: The use of salivary diagnostics to measure SAA offers a cost-effective, non-invasive method for assessing metabolic health. This approach has the potential to be applied in large-scale population studies and clinical settings for early identification of individuals at risk for metabolic disorders.

6 Comprehensive Dietary Monitoring: Despite the limitations of self-reported food diaries, the study implemented weekly dietary monitoring, which allowed for detailed tracking of dietary adherence and provided valuable data on the impact of dietary interventions.

7 Focus on Women of Reproductive Age: By targeting overweight women of reproductive age, the study addresses a population that is particularly vulnerable to

metabolic disorders, such as insulin resistance and visceral obesity. This focus contributes to the understanding of metabolic health in a critical demographic group.

The study is limited by:

1 Population Specificity: The exclusive focus on overweight women of reproductive age limits the applicability of the results to other populations, such as men, postmenopausal women, or individuals with different health profiles. This narrow demographic scope may not capture the full spectrum of metabolic responses across diverse populations.

2 Sample size and Statistical Power: The relatively small sample size, particularly in the control group, may have reduced the statistical power of the study and increased

3 Bioimpedance Analysis: Visceral fat percentage was measured using the Omron BF511 bioimpedance scale, which relies on proprietary algorithms. While bioimpedance analysis is a widely used and non-invasive method, it is less precise compared to gold-standard techniques such as dual-energy X-ray absorptiometry (DXA) or magnetic resonance imaging (MRI). This limitation may have introduced variability in the measurement of visceral fat, potentially affecting the accuracy of the results.

4 Causality: Although the study identified associations between salivary amylase activity, visceral fat, and glucose homeostasis, the evidence does not establish direct causality. The observational nature of the study design limits the ability to infer causal relationships between these variables.

5 Microbiome Analysis: The lack of direct microbiome profiling limits the ability to fully elucidate the relationship between salivary amylase activity, gut microbiota composition, and butyrate production. This gap restricts the mechanistic understanding of how dietary interventions may influence metabolic outcomes through microbiota-mediated pathways.

16 Potential Biases

- Selection Bias: The inclusion criteria focused on overweight women without chronic diseases or medications affecting metabolic outcomes, which may limit the applicability of findings to individuals with more complex health profiles.
- Reporting Bias: Dietary adherence was monitored through self-reported weekly food diaries, which are prone to inaccuracies, underreporting, or recall bias.

Future studies should aim to address these limitations by incorporating larger, more diverse populations, direct microbiome profiling, and more objective methods of dietary adherence monitoring, such as digital tracking tools or biomarkers of dietary intake. By mitigating these biases, the robustness and generalizability of the findings can be improved.

17 Future Directions

To deepen understanding of salivary amylase activity (SAA) as a modulator of metabolic health, future research should employ integrative approaches combining genetic, physiological, and molecular analyses across diverse populations.

17.1 Postprandial Glucose–Insulin Dynamics

Future studies should examine how SAA influences postprandial glycaemic and insulinemic responses through modulation of starch hydrolysis and glucose absorption. Continuous glucose monitoring and standardised meal tests, stratified by SAA activity, would enable precise characterisation of glucose–insulin kinetics and enzymatic variability.

17.2 Genetic and Autonomic Regulation

Precise quantification of *AMY1* gene copy number through advanced genomic sequencing techniques is critical to unravel the genetic determinants of salivary amylase (SAA) production and its role in driving metabolic variability among individuals. Concurrently, the integration of autonomic regulatory assessments – utilising heart rate variability (HRV) and salivary cortisol levels as biomarkers – offers a unique opportunity to explore the influence of sympathetic nervous system activation on SAA secretion. This dual approach could provide novel insights into the interplay between genetic predisposition and autonomic control in shaping SAA-mediated metabolic pathways and their downstream physiological effects.

17.3 Microbiome and Gut–Oral Axis Interactions

Advanced microbiome profiling techniques, such as 16S rRNA sequencing and metagenomic analysis, should be employed to investigate the interplay between salivary amylase (SAA) activity, gut microbial composition, and the production of short-chain fatty acids (SCFAs). These studies would provide critical insights into how starch availability and microbial fermentation modulate systemic insulin sensitivity and inflammatory responses. Furthermore, experimental studies focusing on the gut–oral axis, including the neural pathways that mediate bidirectional communication between the oral cavity and gastrointestinal tract, are essential to elucidate the mechanistic links underlying these interactions.

17.4 Interventional and Causal Designs

Causality should be tested through pharmacological and dietary interventions that modulate SAA secretion or activity. Controlled feeding studies with varying starch content, glycaemic load, or prebiotic supplementation would reveal metabolic outcomes associated with differing SAA levels and their effects on butyrate production and insulin sensitivity.

17.5 Validation in Diverse Populations

Replication of findings in larger, demographically diverse cohorts – including men and individuals of varying age and ethnicity, is needed to assess population-specific associations and improve translational relevance. Multicentre trials with stratified analyses are recommended.

17.6. Long-Term and Personalised Dietary Interventions

Longitudinal studies (≥ 1–5 years) are required to evaluate the durability and clinical significance of SAA-tailored dietary strategies, including effects on diabetes risk, cardiovascular health, and quality of life.

17.7 Molecular Mechanisms and Hormonal Pathways

Mechanistic research should elucidate molecular links between SAA activity, GLP-1 secretion, and glucose homeostasis. In vitro and in vivo models examining SAA-derived oligosaccharides and enteroendocrine signalling will provide mechanistic insight into SAA-mediated regulation of insulin sensitivity and lipid metabolism.

Conclusions

This study provides significant insights into the role of salivary amylase activity (SAA) in modulating metabolic health, particularly in overweight women of reproductive age. The findings demonstrate that dietary interventions, specifically calorie-restricted (CR) and low-starch (LS) diets, lead to distinct improvements in metabolic markers, with the response being influenced by individual variations in SAA.

Participants with high salivary amylase activity (HSA) showed greater improvements in insulin sensitivity and reductions in visceral fat percentage when following a calorie-restricted diet. Conversely, those with low salivary amylase activity (LSA) exhibited enhanced glycaemic control and significant increases in active GLP-1 levels when adhering to a low-starch diet. These results highlight the differential metabolic responses to dietary interventions based on SAA levels, emphasising the potential of SAA as a biomarker for personalised nutrition strategies.

The study also revealed that visceral fat plays a critical mediating role in the relationship between SAA and the triglyceride-glucose (TyG) index, accounting for 45 % of the total effect. This underscores the importance of targeting visceral adiposity in metabolic health interventions. Furthermore, reductions in leptin levels and improvements in insulin sensitivity were observed, particularly in the HSA-CR group, while the LSA-LS group demonstrated significant changes in GLP-1 secretion and C-peptide levels.

These findings suggest that SAA could serve as a non-invasive biomarker for early identification of individuals at metabolic risk and for guiding personalised dietary interventions aimed at reducing insulin resistance and preventing obesity-related complications. The study also highlights the need for further research to explore the long-term effects of dietary interventions, the genetic and hormonal regulation of SAA activity, and the molecular mechanisms underlying its impact on metabolic health.

Although the evidence remains correlational, SAA activity holds promise as a biomarker for metabolic health and appetite regulation. Future studies should focus on elucidating causal mechanisms.

This research contributes to the growing body of evidence supporting the role of SAA in metabolic regulation and emphasises the importance of personalised nutrition strategies tailored to individual enzymatic profiles. By integrating SAA as a biomarker into clinical practice, it may be possible to optimise dietary interventions and improve metabolic health outcomes in vulnerable populations, such as overweight women of reproductive age.

Proposals

1 Personalised dietary recommendations

- Women with high salivary amylase activity (SAA) may benefit from calorie-restricted diets, which can enhance insulin sensitivity and reduce visceral adiposity.
- Women with low SAA achieve better glycaemic control with low-starch diets, which help reduce postprandial glycaemic excursions and increase butyrate.

2 SAA as an early biomarker

The assessment of salivary amylase activity may serve as an early diagnostic tool for identifying individuals who require tailored, personalised nutritional strategies aimed at improving glycaemic control and reducing metabolic risk.

Future perspectives:

- Integrating SAA measurement into a comprehensive metabolic risk assessment panel, combining it with other salivary biomarkers, including hormones (e. g. cortisol), inflammatory cytokines (IL-6, TNF-α), and adipokines (leptin, adiponectin, etc.).
- Incorporating modern biosensor technologies, such as intraoral sensors with wireless data transmission and smartphone interfaces, to enable real-time monitoring of metabolic parameters, stress responses, inflammatory status, and hormone dynamics in ambulatory settings.
- Embedding artificial intelligence (AI) algorithms into biosensor platforms to transform raw physiological signals into clinically actionable information, improving metabolic health assessment and supporting personalised therapeutic decisions.

3 Prioritising visceral fat reduction for metabolic health

Metabolic health strategies should emphasise reducing visceral adiposity – a key determinant of insulin resistance – rather than relying solely on body mass index (BMI) as a clinical indicator.

4 Future research directions

- Future studies should focus on the long-term effects of dietary interventions, including their impact on gene expression related to lipid metabolism, inflammation, and insulin signalling pathways.
- Additional research is required to clarify the molecular mechanisms through which salivary amylase activity and dietary interventions influence metabolic biomarkers.

- Studies should examine AMY1 gene copy number variation and hormonal regulators (e. g. cortisol) that modulate SAA and associated metabolic health indicators.
- Research should be expanded to diverse populations (men, and women outside reproductive age) to evaluate the generalizability of findings.
- Comprehensive gut microbiome profiling is recommended to better understand the interactions between SAA, microbial composition, and metabolic health.

List of publications, reports and patents on the topic of the Thesis

Publications:

1. Erta, G., Gersone, G., Jurka, A., & Tretjakovs, P. (2024). Impact of a 12-Week Dietary Intervention on Adipose Tissue Metabolic Markers in Overweight Women of Reproductive Age. *International Journal of Molecular Sciences*, *25*(15), 8512. https://doi.org/10.3390/ijms25158512
2. Erta, G., Gersone, G., Jurka, A., & Tretjakovs, P. (2024). The Link between Salivary Amylase Activity, Overweight, and Glucose Homeostasis. *International Journal of Molecular Sciences*, *25*(18), 9956. https://doi.org/10.3390/ijms25189956
3. Erta, G., Gersone, G., Jurka, A., & Tretjakovs, P. (2025). Decoding metabolic connections: the role of salivary amylase activity in modulating visceral fat and triglyceride glucose index. *Lipids in Health and Disease*, *24*(1), 98. https://doi.org/10.1186/s12944-025-02524-7
4. Erta, G., Gersone, G., Jurka, A., & Tretjakovs, P. (2025). Salivary α-Amylase as a Metabolic Biomarker: Analytical Tools, Challenges, and Clinical Perspectives. *International Journal of Molecular Sciences*, *26*(15), 7365. https://doi.org/10.3390/ijms26157365
5. Erta G, Gersone G, Jurka A, Tretjakovs P. Salivary amylase activity: A potential modulator of glucose homeostasis, insulin secretion, and appetite regulation. *J Nutr Biochem*. 2025 Oct 21; 148:110154. https://doi.org/10.1016/j.jnutbio.2025.110154

Reports and theses at international congresses and conferences:

1. Erta, G., Gersone, G., & Tretjakovs, P. (2023). Telehealth and metabolic health: Unraveling the effects of a 12-week low-starch diet on HOMA2-B and insulin resistance in overweight women. *Journal of the Endocrine Society*, 7(Supplement_1), bvad114.127. https://doi.org/10.1210/jendso/bvad114.127 Research output: Contribution to journal › Meeting abstract › Peer-reviewed
2. Erta, G., Gersone, G., & Tretjakovs, P. (2023). What is found from placing a continuous glucose monitor in overweight non-diabetic reproductive-age women with insulin resistance? *Medicina* (Kaunas), 59(Suppl. 2), 46. Research output: Contribution to journal › Meeting abstract › Peer-reviewed
3. Erta, G., Gersone, G., & Tretjakovs, P. (2022). Does phase angle analysis in overweight women be a surrogate marker of insulin resistance? Endocrine Abstracts, 83, DOMNP1. Research output: Contribution to journal › Meeting abstract › Peer-reviewed

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2. Al-Akl, N., Thompson, R. I., & Arredouani, A. (2022). Elevated levels of salivary α- amylase activity in saliva associated with reduced odds of obesity in adult Qatari citizens: A cross-sectional study. *PloS One*, 17(3), e0264692. https://doi.org/10.1371/journal.pone.0264692

3. Ali, M. M., Phillips, S. A., & Mahmoud, A. M. (2020). HIF1α/TET1 Pathway Mediates Hypoxia-Induced Adipocytokine Promoter Hypomethylation in Human Adipocytes. *Cells*, 9(1), 134. https://doi.org/10.3390/cells9010134

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