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Review: Obesity Induced Insulin Resistance, Type 2 Diabetes and Emerging Therapeutic Approaches

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1. Abstract

There is a strong association between obesity, insulin resistance and type 2 diabetes mellitus. Abdominal obesity appears to be a major mediator of insulin resistance and hyperinsulinemia. Insulin resistance is a pathological condition in which cells fail to respond normally to the hormone insulin leading to high blood sugar (impaired glucose uptake in peripheral tissues, particularly in skeletal muscle.) The more life-threatening problems fall into four main areas: type 2 diabetes, cardiovascular diseases (CVD), dyslipidemia and certain types of cancers and musculoskeletal disorders.

There is considerable evidence that inflammation is a primary mediator of obesity induced insulin resistance and related co-morbidities, including diabetes and CVD whereby pro-inflammatory substances and other chemokines produced by adipocytes and macrophages are able to cause insulin resistance. The major inflammatory factors include pro-inflammatory interleukins (IL-1 & IL-6) and signaling intermediate-nuclear factor kappa B cells (NF-kB), chemokines and cytokines, tumor necrosis factor alpha (TNF-α), adiponectin (ADN), circulating C-reactive protein (CRP) concentrations, toll-like receptors (Tlr), free fatty acids (FFA), oxidative stress and dietary fatty acids.

Considering this viewpoint, in the present review, we have selected ten well designed clinical studies with salsalates, thiazolidinediones (TZD) and TNF-α–antagonists to discuss and analyze these emerging therapeutic approaches for the treatment of obesity induced insulin resistance and type 2 diabetes mellitus. These therapeutics provide sufficient evidence of improved glycemic control post treatment in obese patients by targeting the state of chronic inflammation that characterizes obesity and resulted in improved insulin sensitivity by reducing adipocyte pro-inflammatory cytokine expression, adipose tissue macrophage content and immune cell infiltration into adipose tissue and other inflammatory markers.

Even with looking at only few studies, analyzing each pathway, the hypothesis that targeting pro-inflammatory pathways in adipocytes with TZD and salsalates as a novel approach remains supported for reducing chronic inflammation-induced insulin resistance in obese patients, with TZD emerging with the strongest effects.

2. Keywords: Obesity; Insulin resistance; Type 2 diabetes; Metabolic syndrome; Pro-inflammatory

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cytokines; Interleukins; Tumor necrosis factor alpha; C-reactive protein; Adipocyte macrophage; Adiponectin; Clinical studies; Salsalates; Thiazolidinediones; Pioglitazone; TNF-α-antagonists; Etanercept

3. Abbreviations:

CVD: Cardio-Vascular Disease; IL: Interleukin; MCP-1: Monocyte Chemoattractant Protein-1; TNF-α: Tumor Necrosis Factor-Alpha; ADN: Adiponectin; CRP: C-Reactive Protein; Tlr: Toll Like Receptor; FFA: Free Fatty Acid; NF-kB: Nuclear Factor kappa-light-chain Enhancer of Activated B Cells; IR: Insulin Receptor; IRS: Insulin Receptor Substrate; PI3K: Phosphoinositide 3-Kinase; Akt/PKB: Protein Kinase B; GLUT4: Glucose Transporter 4; TZD: Thiazolidinediones; BMI: Body Mass Index; QTL: Quantitative Trait Locus; ROS: Reactive Oxygen Species; SAA: Serum Amyloid A; HbA1c: Glycosylated Hemoglobin; HOMA-B: Homeostatic Model Assessment of Beta-Cell Function; AUC: Area Under Curve; OGTT: Oral Glucose Tolerance Test; HGP: Hepatic Glucose Production; GIR: Glucose Infusion Rate; PAI-1: Plasminogen Activator Inhibitor-1; EGP: Endogenous Glucose Production; iNOS: Inducible Nitric Oxide; sICAM: Soluble Intercellular Adhesion Molecule-1; PPAR-γ: Peroxisome Proliferator-Activated Receptor Gamma; HMW: High Molecular Weight

4. Introduction

Since 1980, the global incidence of overweight and obesity has risen to the extent that almost one-third of the world population is now considered being overweight or obese [1]. Obesity is a heterogeneous condition deriving from genetic and lifestyle interactions and energy imbalance [2-7] and is correlated with several pathological dysfunctions with important consequences for individual and community health [8,9]. Worldwide, it was estimated that more than 1.9 billion adults and 41 million children were overweight in 2014 including 18 years and above, out of which 600 million were obese [7,10].

The excessive accumulation of body fat, particularly around the abdominal area, characterizes the state of obesity, a medical condition that can lead to various co-morbidities [1,11,12]. The more life-threatening problems related to obesity include cardiovascular problems including heart disease and stroke - the leading cause of death, dyslipidemia, certain types of cancers (endometrial, breast, ovarian, prostate, liver, gall bladder, kidney and colon) and musculoskeletal disorders (especially osteoarthritis) [1,7,10,12-17]. Furthermore, abdominal obesity particularly serves as a major contributing factor for the development of insulin resistance and hyperglycemia that characterizes diabetes, metabolic syndrome and non-alcoholic fatty liver [16,18-41]. Insulin resistance results when normal cellular responses to insulin fail by overproduction of insulin (hyperinsulinemia) by pancreatic beta cells that can no longer regulate glucose metabolism [42,43]. Insulin resistance is a fundamental aspect of the etiology of type 2 diabetes, one of the leading causes of preventable deaths. The reasons of its dramatic increase can be attributed to changes in lifestyle, increasing prevalence of obesity and ageing of populations [3,4]. The incidence of obesity-induced diabetes is estimated to reach pandemic levels, doubling in a period of only thirty years (from 171 million in 2000 to 366 million in 2030) [44,45].

Furthermore, there is considerable evidence that inflammation is a primary mediator of obesity induced insulin resistance and related health problems, including diabetes and CVD [46-52]. Obesity is also known to be a condition of chronic inflammation whereby pro-inflammatory substances and other chemokines produced by adipocytes and macrophages are able to cause insulin resistance [53-63]. The major inflammatory factors include pro-inflammatory cytokines (interleukins-IL) such as IL-1 & IL-6 [63-67], chemokines and cytokines such as MCP-1 [67-69], tumor necrosis factor-alpha (TNF-α)

[70-73] and adiponectin (ADN) [74-78]. Other pro-inflammatory substances involved in the development of obesity induced insulin resistance and co-morbidities are circulating C-reactive protein (CRP) concentrations [46,48,58,79-81], toll like receptor (Tlr) [82-84], free fatty acid (FFA) [85-89], oxidative stress [90-96] and dietary fatty acids [91,97,98].

Interleukins activate specific pro-inflammatory signaling intermediates such as pro-inflammatory transcription factor- nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) which hinder insulin signaling [99-103]. Specifically, IL-6 was observed to inhibit autophosphorylation of the insulin receptor (IR) and downstream effectors including insulin receptor substrate-1/2 (IRS-1/2), phosphatidylinositol-3 kinase (PI3K), protein kinase B (Akt/PKB) and glucose transporter-4 (GLUT4) [99,102,103]. TNF-α signaling impairs insulin signaling, in part through serine phosphorylation of IRS-1 and IRS-2 and can reduce insulin-regulated GLUT4 which is located mainly in adipocytes and skeletal and cardiac muscles [70,104-107].

Insulin resistance in obesity and type 2 diabetes is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output [13,109]. A leading hypothesis in this regard is that intra-abdominal adipocytes are more lipolytically active and increase intra-portal FFA levels and flux, which might inhibit insulin clearance and promote insulin resistance [59,87]. Hyperinsulinemia per se can cause insulin resistance by down regulating insulin receptors and desensitizing post-receptor pathways. An alternative hypothesis states that adipocytes secrete many factors that are capable of exerting systemic effect and may be harmful to systemic insulin sensitivity [56,57]. Moreover, the inflammatory state of obesity leads to increased infiltration of immune cells, including adipose tissue macrophages and T cells, into the metabolic tissues [110]. Immune cell-derived cytokines and chemokines augment metabolic tissue inflammation, inducing obesity related insulin resistance and type 2 diabetes [51].

Thus, in the present review, we have selected ten well designed clinical studies with salsalates, thiazolidinediones (TZD) and TNF-α–antagonists, addressing above issues, to discuss and analyze these emerging therapeutic approaches for the treatment of obesity induced insulin resistance and type 2 diabetes mellitus.

5. Inflammatory Markers

Cytokines

Interleukins (IL)

Pro-inflammatory cytokines are small proteins that are increased with obesity [66,67]. These are produced by adipocytes and macrophages that are reported to cause insulin resistance [63]. As a result of this stimulation, the pro-inflammatory transcription factor NF-kB is activated leading to downstream release of IL-6, IL-1 and IL-1 dependent cytokines, resulting in a state of inflammation [101] and is important in the pathogenesis of insulin resistance and type 2 diabetes [53,56,64,75,99,100,110-113].

Chemokines

Monocyte Chemoattractant Protein-1 (MCP-1)

These chemokines are small proteins similar to cytokines, which also exhibit the ability to induce chemotaxis. Obesity is associated with increased circulating monocyte chemoattractant protein-1 (MCP-1) [67,69]. Recent work [55] has shown that a high concentration of circulating MCP-1 was associated with insulin resistance and diabetes.

Tumor Necrosis Factor-Alpha (TNF-α)

In obesity, adipose tissue itself is a site of inflammation [63]. This is attributed to increased production of tumor necrosis factor-alpha (TNF- α) and inflammatory cell infiltrate in stressed adipose tissue [54,58,73,114-116]. Elevated TNF-α levels are closely related to components of metabolic syndrome including impaired glucose tolerance, insulin resistance, hypertension and dyslipidemia in obese

adults, adolescents and elderly patients [53,61,64,70-72,75,117].

Adiponectin (ADN)

Adiponectin (ADN), the most abundant peptide secreted by adipocytes, is a major regulator of glucose and lipid homeostasis via its insulin-sensitizing properties and lower levels seems to be associated with the development of type 2 diabetes and metabolic syndrome [57-59,74,75,77,118]. Obesity is also associated with reduced concentrations of ADN. Several genetic analyses [78,119] observed that a quantitative trait locus (QTL) on chromosome 3 (3q27), the site of the ADN gene, was strongly correlated with insulin resistance, metabolic syndrome and diabetes, body mass index (BMI) and waist circumference [118].

C-Reactive Protein (CRP)

There is considerable evidence that inflammation is a primary mediator of obesity induced insulin resistance, type 2 diabetes and cardiovascular diseases. [46,49,61]. Circulating C-reactive protein (CRP) concentrations, common clinical indicators of systemic inflammation, were found higher in populations with metabolic syndrome and diabetes [46,48,58,80,81].

Toll-like Receptor (Tlr)

Toll-like receptors (Tlr2 and Tlr4) are germline-encoded receptors expressed on a variety of innate immune cells and are known inducers of inflammation, obesity, insulin resistance and type 2 diabetes [82,120-122]. There is substantial evidence that the innate immune receptor is a major mediator of obesity-induced insulin resistance [109].

Oxidative Stress

Obesity-induced oxidative stress represents a potential link between obesity and its associated diseases. Reactive Oxygen Species (ROS) are small, highly reactive molecules possessing oxidative abilities primarily attributed to an unpaired electron [93]. Several investigations have indicated the role of oxidative damage in atherosclerosis, hypertension, diabetes and obesity [90-93]. The increased oxidative stress associated with obesity is specifically linked to the development of insulin resistance [16,53,94,96].

Free Fatty Acid (FFA)

Multiple investigations have demonstrated an increase in circulating free fatty acids (FFA) in obese humans [123]. Obesity-related insulin resistance and co-morbidities, including diabetes and cardiovascular diseases, have also been directly associated with increased FFA [30,85-89,100,124-127].

Dietary Fatty Acid

The saturated fatty acid may be responsible for the increase in pro-inflammatory cytokines and chemokines observed with obesity and metabolic syndrome [91,97,98,128]. The consumption of a Westernized diet high in refined grains, red meat, saturated fatty acid and hydrogenated fats has been positively related to several markers of inflammation including CRP, serum amyloid A (SAA) and IL-6 [129]. Moreover, saturated fatty acid intake is specifically linked to the development of inflammation and insulin resistance through different pathways in humans.

6. Materials and Methods

General Search Strategy

Literature search was performed using Google Scholar as well as PubMed databases. To learn about the broad topic of insulin resistance and obesity, a general search on Google and Google Scholar was first carried out. Epidemiological data was collected from visiting the World Health Organization website and also from the Journal of the American Medical Association. To develop the topic and for background information in the introduction, both review and primary papers were used. Though, specific findings were cross-referenced from review papers such that the primary paper from which the data was obtained is cited. Only primary papers were used for the development of the results and discussion. Relevant articles were also found from the 'References' section of other articles. Filters were used to narrow down the

searches to more relevant articles. Specific exclusion and inclusion criteria were used to narrow down the searches to studies more relevant to the topic being discussed.

7. Results

Group I. Treatment with Salsalates

Study 1: Goldfine et al. 2013

In a randomized, parallel, double-blind and placebo-controlled 8 and 12 weeks, two centre trial, Goldfine et al. 2013 [130] studied the effects of salsalate on insulin resistance, glycemia and inflammation. Significant reduction in fasting glucose ($p<0.05$; $p<0.01$) and C-peptide levels ($p<0.05$; $p<0.01$; $p<0.001$) followed by marked increase in ADN level ($p<0.005$) and reduced adipose tissue NF-κB activity ($p<0.05$; $p<0.01$) was noticed with salsalate as compared to placebo, as well as compared within groups, showing the improvement of insulin sensitivity. But no change in fasting insulin levels ($p>0.05$) was found at the end of the study (Figure 1 and 2).

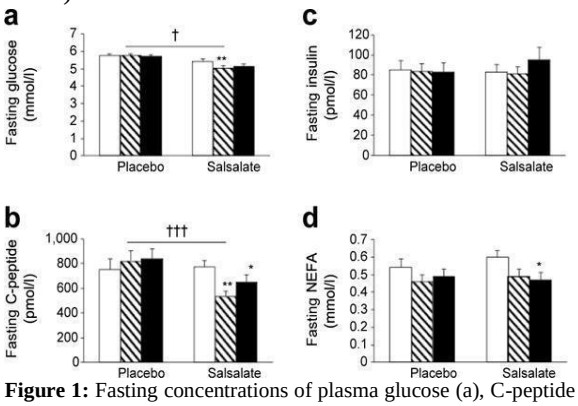


Figure 1: Fasting concentrations of plasma glucose (a), C-peptide (b), insulin (c) and non-steroid fatty acid (NEFA) (d). Data are means ± SE. *p< 0.05, **p< 0.01, within group comparison of week 8 (hatched bars) or week 12 (black bars) vs baseline (white bar); †p< 0.05, †††p< 0.001, placebo vs salsalate; repeated measures ANCOVA adjusted for site **[Study 1: Goldfine et al. 2013].**

Study 2: Kim et al. 2014

Kim et al. 2014 [131] analyzed the effects of salsalate on insulin action, secretion and clearance in non-diabetic, insulin-resistant obese individuals. The study was randomized, single-blinded, parallel and placebo-controlled. It was found that fasting plasma glucose was lower in the salsalate treatment group ($p=0.004$) and did not directly affect insulin secretion, as observed (Figure 3), indicating that salsalate indirectly decreases the clearance rate of insulin. This finding is similar to that of Study 1 [132].

Study 3: Faghihimani et al. 2013

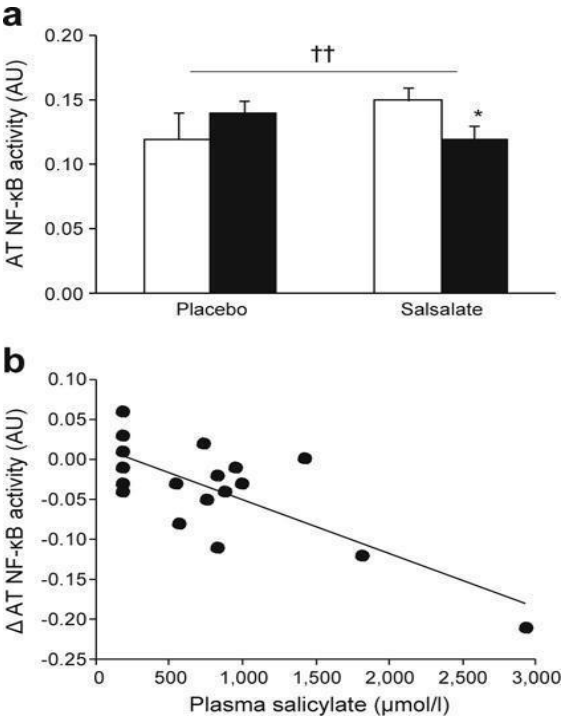


Figure 2: (a) NF-κB activity in the subcutaneous abdominal adipose tissue (AT) at baseline (white bars) and after 12 weeks' (black bars) treatment with salsalate or placebo. Data are means ± SE; *p< 0.05, week 12 vs baseline; ††p< 0.01, salsalate vs placebo; repeated measures ANCOVA adjusted for site. (b) Spearman correlation between follow-up plasma salicylate levels and change (follow-up minus baseline) in adipose tissue NF-κB activity ($r=-0.53$, $p=0.02$). AU, arbitrary units **[Study 1: Goldfine et al. 2013].**

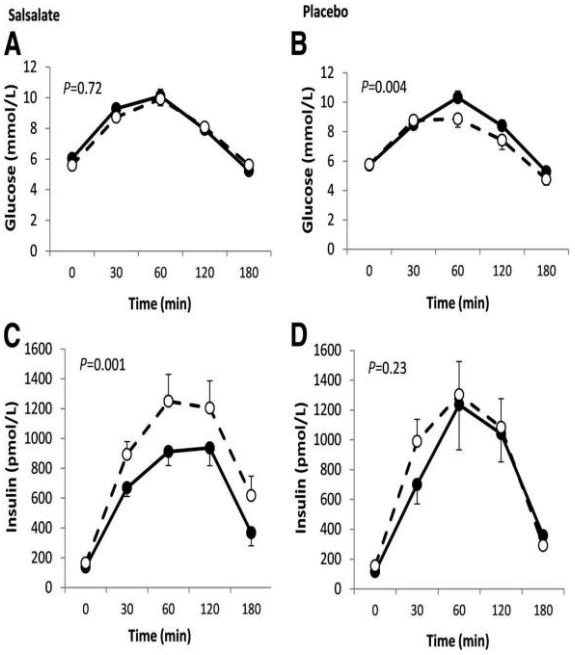
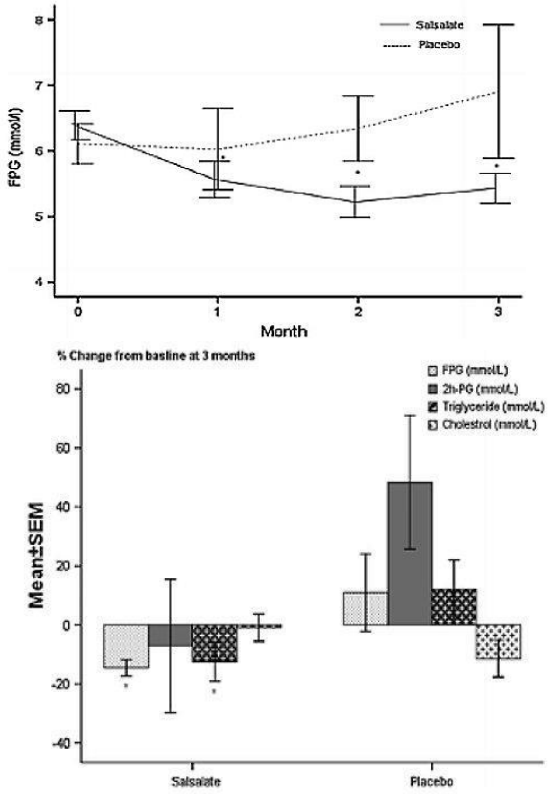


Figure 3: Changes during the OGTT in glucose (A and B) and

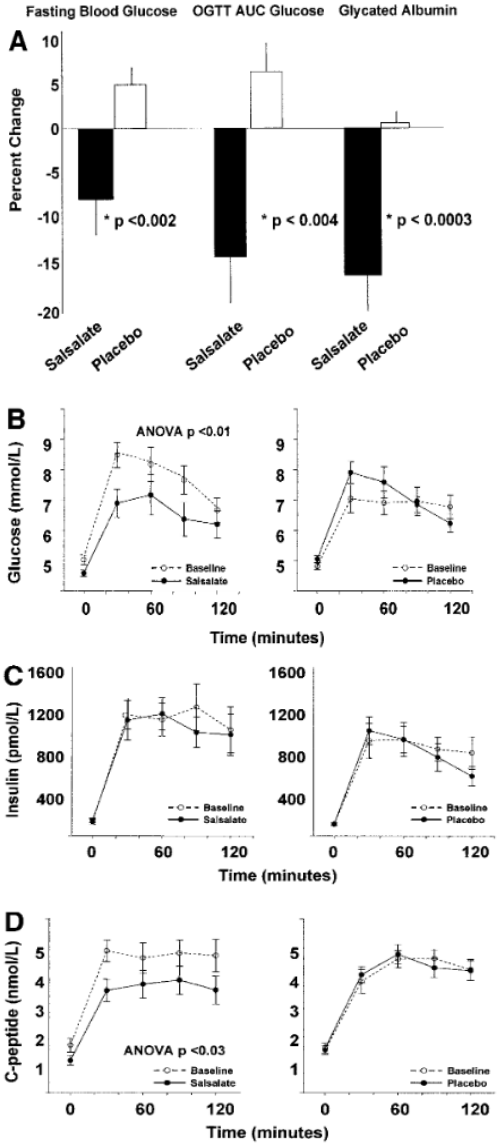
insulin (C and D) profile following salsalate (A and C) and placebo (B and D) treatment. Curves at baseline (closed circles) and 4 weeks (open circles) after treatment are shown. Glucose AUC was



significantly lower after placebo (p=0.004) and insulin AUC was significantly higher after salsalate (p=0.001). 'p' values represent within-group difference in AUC **[Study 2: Kim et al. 2014].**

Figure 4: (A and B): Effect of salsalate on fasting plasma glucose level as compared to placebo; *p< 0.01 in 2- and 3-months period of time. (B): Changes in 2-hour plasma glucose level as compared to placebo; p<0.29. Unpaired and paired t-tests were used to make group comparisons along with ANOVA and p<0.05 was used to determine statistical significance. **[Study 3: Faghihimani et al. 2013].**

Faghihimani et al. 2013 [132] studied the effects of salsalate on glucose control in patients with type 2 diabetes, in a double-blind study, specifically targeting inflammatory pathways that interfere with insulin action leading to insulin resistance. Salsalate significantly reduced fasting glucose (p<0.01) as compared to placebo in 2nd and 3rd months period of the study (Figure 4). This is similar to the findings reported in Study 2 [131]. Even though salsalate treatment resulted in a decrease in the 2-hour plasma glucose level, this result was not statistically significant (p<0.29). But in the groups of plasma insulin, glycosylated haemoglobin (HbA1c) and homeostatic model assessment of β-cell function (HOMA-B), there were significant changes in-



between, indicating improved glycemic control (p<0.04; p=0.06) in newly diagnosed naive patients with type 2 diabetes mellitus [33].

Figure 5: A: Fasting glucose (*p<.002), AUC after an OGTT (*p<0.004) and glycated albumin (*p<0.0003) in salsalate-treated subjects compared with the placebo group. B: Improvements in glycemia after an OGTT by salsalate compared to placebo. C and D: No significant changes in levels of fasting insulin (C) and C-peptide (D). Mean and SEM data are shown before and 30, 60, 90 and 120 min after 75g oral glucose. **[Study 4: Fleischman et al. 2008].**

Study 4: Fleischman et al. 2008

To further study the effectiveness of salsalates in controlling inflammatory parameters to improve

glycemia, Fleischman et al. 2008 [133] conducted a double-blind, placebo-controlled trial with non-diabetic subjects aged <30 years and a BMI of ≥30 kg/m^2. There was 13% reduction (p<0.002) in fasting glucose, 17% in glycated albumin (p<0.0003) and marked decrease in OGTT (p<0.004) following salsalate treatment in comparison with placebo. Subjects in the salsalate treatment group also had a reduced glucose area under curve (AUC) after a 75g oral glucose tolerance test (OGTT) in comparison with placebo (Figure 5A, 5B). These results indicate increased insulin sensitivity due to decreased insulin clearance. But no significant changes in fasting insulin and C-peptide levels were observed (Figure 5C, 5D). Salsalates significantly increased ADN levels (57%; p<0.003) and reduced CRP (34%; p<0.05) and FFA (p<0.05) [133] in comparison to placebo, indicating the role of salsalates in improving glycemia through their anti-inflammatory effects (Figure 6A, 6B).

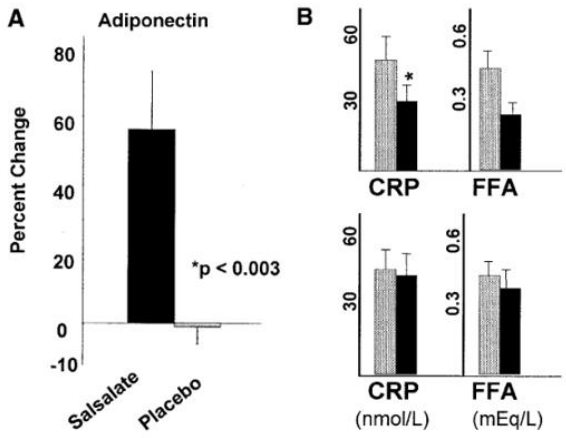


Figure 6: Changes in inflammatory markers and mediators. A: Adiponectin increased significantly in the salsalate-treated group compared with the placebo group (*p<0.003). B: CRP and FFA were lower after salsalate (upper panel) but unchanged after placebo (lower panel) by within-group analysis (*p< 0.05). ▨, baseline; ■, after therapy **[Study 4: Fleischman et al. 2008].**

Study 5: Alderete et al. 2015

In a randomized double-blind, placebo-controlled trial in non-diabetic obese Hispanic subjects, salsalate treatment reduced fasting blood glucose by 3.4% (p<0.01; Figure 7A) and fasting FFA (p=0.02; Figure 7C) followed by decrease in median blood glucose (p<0.01) and median blood FFA levels (−42.5%, p=0.06) [135]. In this study, increased insulin AUC (p = 0.01), median insulin value (p = 0.01) and HOMA-B (p<0.01) were observed while estimates of direct insulin sensitivity/resistance (estimated by HOMA-IR, QUICKI or Matsuda Index) were unaffected [134]. Although there was a trend for an increased fasting C-peptide in the placebo group, salsalate treatment did not significantly alter levels of fasting insulin and fasting C-peptide (Figure 7B,7D). Fasting insulin to C-peptide ratios were also increased in the salsalate (P<0.01). Similar to the findings reported by other investigators [130,133], an increase in ADN levels (27.7%; p< 0.01) was also found as compared to placebo [134].

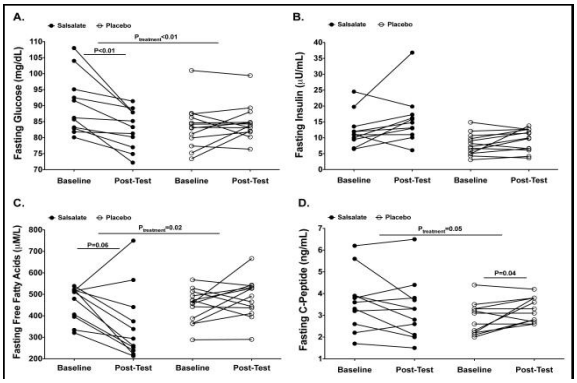


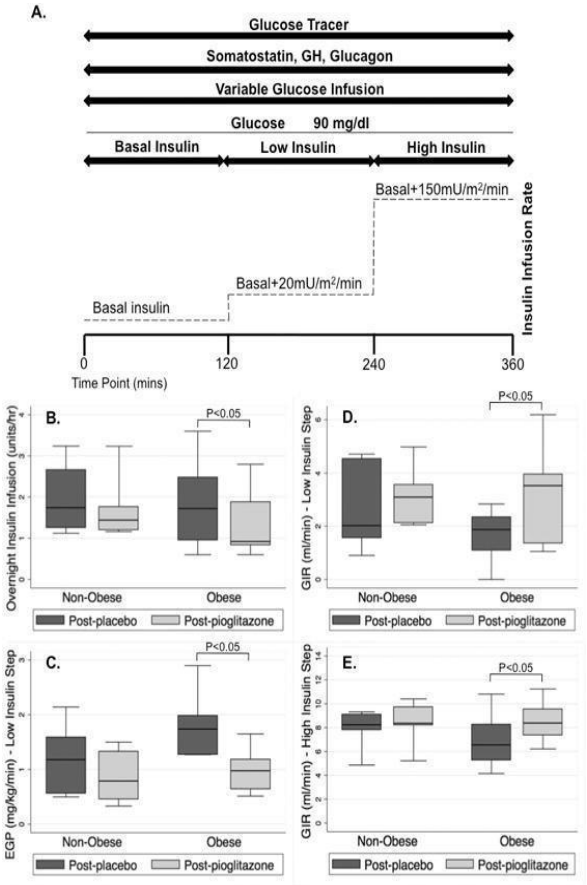
Figure 7: Fasting Measures From the 2-hr OGTT. Fasting glucose; p<0.01 (A), insulin; not significant (B), free fatty acids; p=0.02 (C) and C-peptide; not significant (D). Individual participant data where black circles = salsalate groups and white circles = placebo. Treatment p-values are from ANCOVA, which controlled for the baseline dependent variable and body fat percent. Within group p-values correspond to Related-Samples Wilcoxon Signed Rank Test **[Study 5: Alderete et al. 2015].**

Group II. Treatment with Thiazolidinediones (TZD; Pioglitazone)

Study 6: Esterson et al. 2013

Esterson et al. 2013 [135] performed a randomized, double-blind, placebo-controlled crossover study in obesity-induced insulin resistance in obese vs. non-obese patients. Insulin sensitivity was measured using the gold standard "stepped" euglycemic-hyperinsulinemic clamp technique. Overnight insulin infusion rate required to maintain euglycemia was significantly lower following pioglitazone in the

obese group (p<0.05) but not in the non-obese group (p=0.85) (Figure 8A, 8B). During the low-insulin phase, hepatic glucose production/endogenous glucose production (HGP/EGP) was markedly



suppressed in the obese group (p<0.05) by pioglitazone compared to insignificant suppression in non-obese group (p=0.09) (Figure 8C).

Figure 8: Effect of pioglitazone. (A) Euglycemic-hyperinsulinemic pancreatic clamp study time course. (B) Overnight insulin infusion rate: obese group (p<0.05) and non-obese group (p=0.85). (C) HGP suppression in low-insulin step of the clamp: obese group (p<0.05) and non-obese group (p=0.09). (D) GIR increase in low-insulin step of the clamp: obese group (p<0.05) and non-obese group (p=0.40). (E) GIR increase in high-insulin step of the clamp: obese group (p<0.05) and non-obese group (p=0.13) **[Study 6: Esterson et al. 2013].**

During the high insulin phase, no significant difference was noticed with HGP. Glucose infusion rate (GIR) required to maintain euglycemia during the low-insulin and high insulin steps was significantly increased with pioglitazone in the obese group respectively (p<0.05) as compared to insignificant non-obese groups (Figure 8D, 8E). PAI-1 (plasminogen activator inhibitor linked with obesity and insulin resistance), iNOS (inducible nitric oxide synthase) expression levels (indicator of macrophage activation in adipose tissue) and expression of adipose tissue dendritic cell markers (DEC-205 and DC-SIGN) were found to be significantly reduced in obese patients [135]. Treatment with pioglitazone also led to increased adipose tissue expression levels of ADN in obese patients compared to placebo (p=0.04) and changes remained nearly insignificant in non-obese patients (p=0.07) [135]. These findings support the efficacy of pioglitazone to improve insulin resistance and reduce adipose tissue inflammation in obese patients with type 2 diabetes.

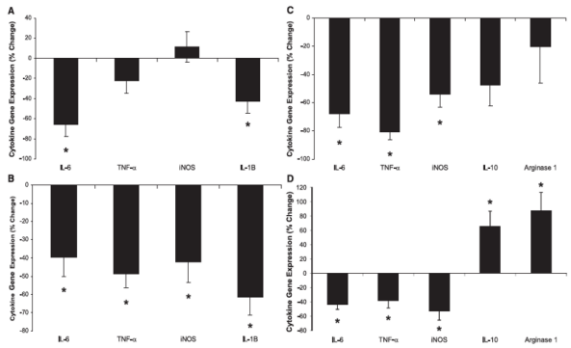


Figure 9: Effect of pioglitazone treatment on cytokine gene expression (% change) in whole fat: A. 10 days B. 21 days. Effect of pioglitazone treatment on cytokine gene expression (% change) in adipose tissue macrophages: C. 10 days D. 21 days. *Significance by p< 0.05 or CI **[Study 7: Koppaka et al. 2013].**

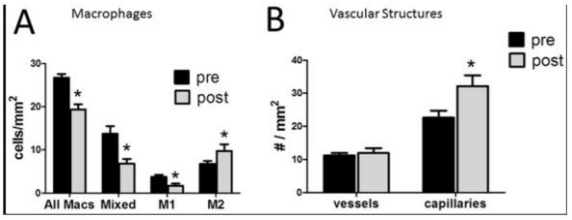


Figure 10: Adipose macrophage polarity and vascularity following pioglitazone treatment. A. Macrophages were characterized as M1, M2, or mixed, pre- and post-pioglitazone treatment. B. Adipose blood vessels were characterized as capillaries, or vessels, based on the absence/presence of ASMA staining of a vessel wall and counted in adipose sections pre- and post-pioglitazone. *p<0.05 vs pre pioglitazone **[Study 8: Spencer et al. 2014].**

Study 7: Koppaka et al. 2013

To study the temporal relationship of the effectiveness of TZD on insulin sensitivity and adipose tissue inflammation, Koppaka et al. 2013 [136] conducted a randomized, double-blind, placebo-controlled crossover study in overweight or obese subjects.

Improved hepatic and peripheral insulin sensitivity was seen after 21 days of pioglitazone treatment as indicated by lower overnight insulin infusion rate ($p<0.03$) and plasma insulin concentrations ($p<0.01$) [136]. Insulin-mediated suppression of EGP was found increased both in low ($p<0.003$) and high insulin phases ($p<0.03$) [136]. Adipose tissue was also assessed for changes in inflammatory marker levels. Pioglitazone treatment for 21 days led to a significant reduction ($p<0.05$) in all of these inflammatory markers (whole-fat IL-6 and IL-1b expression levels, TNF-α or iNOS expression) (Figure 9).

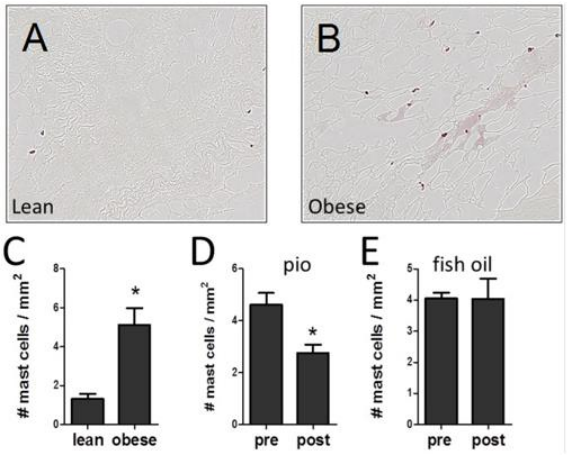


Figure 11: Quantitation of mast cells in adipose tissue. Mast cells were identified in adipose tissue by staining for tryptase in a representative (A) lean and (B) obese subject. C. Quantitation of mast cells in adipose tissue of lean and obese subjects ($p^*<0.05$). D. Mast cells in adipose tissue pre- and post-pioglitazone ($p^*<0.01$). E. Mast cells pre- and post-fish oil treatment (positive control; not significant) [**Study 8: Spencer et al. 2014].**

Study 8: Spencer et al. 2014

To study the long-term effects of pioglitazone treatment on adipose tissue inflammation, Spencer et al. 2014 [137] examined adipose tissue biopsies from obese insulin-resistant individuals in a non-randomized, open clinical trial for 12 weeks. The authors reported an increase in insulin sensitivity from 1.6 to 2.3 units ($p<0.01$) and a decrease in postprandial glucose from 161 mg/dL to 127 mg/dL ($p<0.05$) post treatment [137]. As shown in (Figure 10A), pioglitazone treatment resulted in a decrease in total macrophages, along with a decrease in M1 and mixed M1/M2 macrophages ($p<0.05$), with a relative increase in M2 macrophages. A significant increase in adipose tissue capillaries ($p<0.05$) was also noticed with no change in larger vessels (Figure 10B).

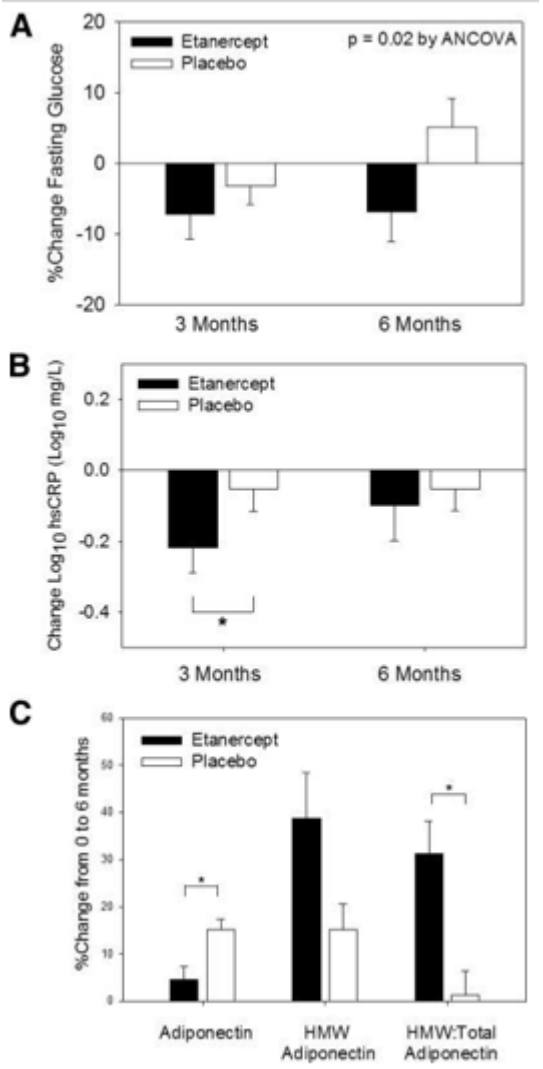


Figure 12: Effect of etanercept. Changes in etanercept (*black bars*) and placebo (*white bars*) groups. Error bars are SE. A: Percent change in fasting glucose at 3 and 6 months; $^*p=0.02$ for etanercept *vs.* placebo by repeated-measures ANCOVA. B: Change in $\log_{10}$ hsCRP at 3 and 6 months. *, $p=0.03$ for change in etanercept *vs.* placebo at 3 months controlling for age and race. C: Aggregate percent change in total adiponectin, HMW adiponectin and ratio of HMW to total adiponectin over 6 months. *, $p< 0.05$ for etanercept *vs.* placebo by repeated-measures ANCOVA **[Study 9: Stanley et al. 2011].**

Pioglitazone treatment further decreased total adipose macrophage number by 26%, with a 56% decrease in M1 macrophages and significant increase in M2 macrophages ($p<0.05$) [137]. The authors also reported that an increased number of mast cells are generally present in adipose tissue of obese versus lean patients ($p<0.05$), which were decreased by

35±9% ($p<0.01$) after treatment with pioglitazone [137; Figure 11A-11C]. As shown in (Figure 11E), fish oil (omega 3-fatty acid) treatment was taken as a positive control to compare with pioglitazone, which did not show any effect on mast cells. Omega 3- fatty acids are known to reduce adipose tissue mast cells.

Group III. Treatment with TNF-α antagonists (Etanercept)

Study 9: Stanley et al. 2011

To study the role of TNF-α- mediated inflammation in obesity-induced insulin resistance, Stanley et al. 2011 [138] conducted a randomized, placebo-controlled, double blind trial using etanercept, a TNF-α inhibitor. Etanercept treatment led to a significant decrease both in fasting glucose levels compared to placebo (−10.8±4.4%, $p=0.02$) and in CRP levels ($p=0.003$) (Figure 12A, 12B). The treatment has also markedly resulted in the increased ratio of high molecular weight (HMW) ADN to total ADN (+22.1 ± 9.2%, $p<0.05$) (Figure 12C) and decreased levels of inflammatory marker-soluble intercellular adhesion molecule-1 (sICAM-1) (-11 ± 2%, $p < 0.0001$) as compared to placebo [138], indicating an improvement in insulin resistance.

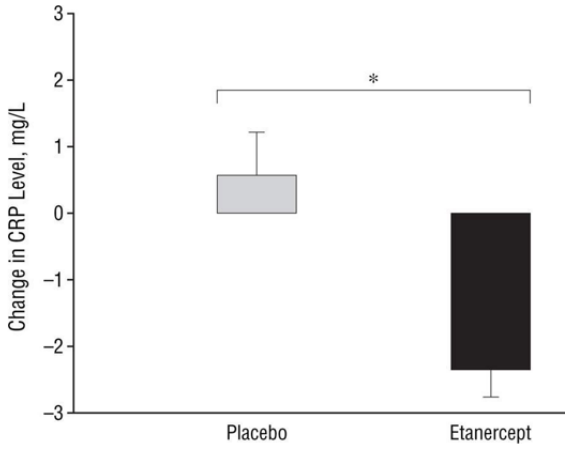


Figure 13: Changes in C-reactive protein (CRP) levels. Results are presented as mean ± SEM (error bars). *p<.001 for comparison of treatment effect from baseline (etanercept vs placebo) using a mixed-model analysis for longitudinal data **[Study 10: Bernstein et al. 2006].**

Study 10: Bernstein et al. 2006

In another trial conducted by Bernstein et al. 2006 [139], the anti-inflammatory effects of etanercept on metabolic improvement were studied in a randomized, placebo controlled double-blinded trial stratified by sex. Etanercept reduces CRP levels and tends to improve other inflammatory cardiovascular risk indexes in patients with metabolic syndrome. Compared to the placebo group, etanercept led to decreased levels of CRP ($p<0.001$) (Figure 13) and increased levels of ADN ($p=0.03$) [139]. Levels of IL-6 showed a downward trend ($p=0.07$) and increased levels of tumour necrosis factor receptor-2 (TNFR-2; ($p<0.01$), which had significant correlation with levels of change in CRP and ADN [139].

8. Discussion

Group 1: Studies on Salsalate Treatment

In Study 1 [130], there is strong evidence for the control of glycemia and metabolic improvement by salsalates in pre-diabetic patients. A reduced insulin clearance was reported but no improvement was seen in insulin sensitivity post treatment when compared with placebo. This result differs from a previous study that suggested high dose aspirin did improve insulin sensitivity in patients with type 2 diabetes [140]. Therefore, the possibility that insulin sensitivity can be improved with salsalates cannot be dismissed. This is an aspect that is incompletely understood and can be studied further as discrepancies may be attributed to differing responses to different doses or whether the patient is pre-diabetic or has established disease [130].

One of the major limitations of Study 1 [130] is the small sample size. A total of 71 participants were randomized of which 37 were allocated to placebo and 34 to salicylate treatment. A bigger sample size could have increased the power of the study. Despite some shortcomings in the study design, Study 1 [130] does provide ample evidence of control of fasting glycemia, triacylglycerols and adipose tissue NF-κB activity post treatment as well as increase in ADN.

In Study 2 [131] there is reported control of fasting plasma glucose in response to salsalate treatment over a shorter period of time. It was found that salsalates

decrease insulin clearance with no effect on actual insulin secretion, similar to that reported in Study 1[130]. Additionally, the small sample size of the study here [131] and subjects being recruited from only one academic center limit the reliability and generalizability of the study to the general population.

In Study 3 [132], further evidence for the improvement of glycemia in subjects treated with salsalates was noticed. The researcher attributed this to either decreased pancreatic islet inflammation mediated by salsalates leading to increased insulin release or decreased insulin clearance. It is possible that it was due to decreased insulin clearance as there was a similar finding in Study 2 [131]. The authors, in the present study [132], retain the possibility of suppression of inflammation mediating improved insulin sensitivity as salsalate is known to inhibit the IKKβ/NF-kB signaling pathways, reducing inflammation [141]. The strength of the present Study 3 [132] lies in the double-blind design and enrolment of drug-naïve subjects recently diagnosed with type 2 diabetes, eliminating confounding factors.

In study 4 [133], salsalates were also found to improve fasting glycemia. Though, improved glycemia was also seen post OGTT in this study, which is in contrast to the results observed in Study 2 [131] and Study 3 [132]. Inflammatory markers such as CRP and FFA levels were also decreased in the present study [133]. It has been earlier confirmed that chronic subclinical inflammation is associated with insulin resistance and central obesity [46]. An improved insulin sensitivity in response to salsalate treatment is reported and attributed to possibly decreased insulin clearance even though it was not directly addressed in the current investigation [133]. A similar finding was also observed by the researchers in Study 2 [131]. In this current Study 4 [133], it was hypothesized that salsalates act through the IKKB/NF-κ B signaling pathways to improve blood glucose levels which is confirmed by the findings of earlier workers [130,141].

Similar to the findings in Study 1 [130], an increased adiponectin level was found post salsalate treatment. The mechanism of action of salsalates, thus, may be mediated through reducing pro-inflammatory cytokines and small pro-inflammatory proteins in adipose tissue and macrophages [70,71]. The strength in Study 4 [133] lies in double-blinding, setting up inclusion criteria (such as excluding patients with concurrent diseases) to eliminate confounding factors and measuring salicylate levels to assess participant compliance.

In Study 5 [134], the authors found improvements in fasting glucose, insulin and FFA levels post treatment with salsalates along with the increase in the ADN levels. These findings were in correlation with those of others [130,133]. But in this study, authors have attributed the rise in ADN to its reduced clearance rather than increased expression by adipocytes, as no change in ADN gene expression was found post salsalate treatment. This was contradictory to a study which found that salsalate led to decreased expression of 11β-hydroxysteroid dehydrogenase type 1 leading to increased expression of ADN in fully differentiated adipocytes [142]. Thus, it is possible that increased levels of ADN could be due to greater expression, translation and secretion of adiponectin or its decreased clearance [143]. Study 5 [134] has limited generalizability due to a very small sample size and inclusion of only Hispanic subjects on a self-report basis.

Overall, there is strong evidence that salsalates improve fasting plasma glucose levels and increase ADN levels.

Even though few discrepancies were noticed in study design related to the subjects recruited, age and gender and study period which might have affected the activity of salsalates in the studies reviewed, the possibility remains that this Group I of treatment [130-134] can be a novel therapeutic approach in the management of obesity-induced inflammation and deregulated glycemia.

Group II: Studies on Thiazolidine diones (TZD; Pioglitazone) Treatment

In Study 6 [135], marked improvement in insulin sensitivity and decreased adipose tissue inflammation post pioglitazone treatment was reported. Most of the beneficial effects of pioglitazone (TZD) in improving insulin sensitivity were found in obese patients. By observing the anti-inflammatory and insulin sensitizing effects, pioglitazone can be an important therapeutic agent to target obesity-induced insulin resistance. Although one of the major side effects of TZD is weight gain [144], there were no changes in the weights of patients in the present Study 6 [135], which could be due to the short duration of treatment. Therefore, it is suggested that studies with larger sample sizes and with strict parameters to define different stages of diabetes (pre-diabetes, diabetes, late-stage diabetes) be conducted for a longer duration. This will allow to further confirm the long-term effects of TZD on obesity-induced insulin resistance and possible side-effects can also be studied.

Study 7 [136] assessed the temporal relationship of the effect of the peroxisome proliferator-activated receptor gamma (PPAR- γ) agonist pioglitazone on insulin sensitivity and adipose tissue inflammation in type 2 diabetic patients. PPAR-γ is a nuclear receptor that is expressed mostly in adipocytes and macrophages and is involved in metabolism of glucose and has insulin-sensitizing and anti-inflammatory effects [145,146]. These views are confirmed by other researchers in the Study 6 [135] who attributed this improvement to a reduction in adipose tissue macrophage content. Thus, the temporal differences in the effects of pioglitazone on insulin sensitivity are justified. It has been further confirmed here [136] that the anti-inflammatory and insulin sensitizing effects of TZD (pioglitazone) can be an important therapeutic agent to target obesity-induced insulin resistance in patients with type 2 diabetes as well. A reduction in dendritic cell marker (obesity-induced macrophage infiltration) found in this study also implies an improvement in adipose tissue inflammation with pioglitazone as reported by earlier researchers [135,136,147,148].

In Study 8 [137], it is suggested that PPAR-γ agonists like TZD reduce inflammation in adipose tissue by mediating macrophage apoptosis [149]. The pioglitazone-mediated significant reduction in mast cells in the obese subjects suggests its efficacy in reducing adipose tissue inflammation through this mechanism as well. Therefore, it is evident that targeting such intracellular pro-inflammatory pathways with anti-inflammatory substances can lead to a reduction in the systemic inflammatory state that characterizes obesity, leading to decreased insulin resistance as well.

Even though the results reported in Study 8 [137] confirm results from previous studies examined [135,136], it can have limited generalization due to a small sample of subjects studied, out of which most subjects were females. The control group did not receive placebo. Further, it is also not clear whether this is a single-blinded study. But, one of the strengths of Study 8 [137] is that it examines the effects of pioglitazone therapy over long term. This study confirms long-term positive effects of pioglitazone treatment on insulin sensitivity and adipose tissue inflammation.

This suggests that TZD can indeed be an effective novel therapy for these patients, targeting insulin resistance mediated by adipose tissue inflammation.

Group III: Studies on treatment with TNF-α antagonists (Etanercept)

Study 9 [138] in Group III, demonstrates that long-term treatment with etanercept can lead to improved glycemia in obese patients which may be due to increased levels of ADN. In previous studies it was reported that levels of adipocyte-adiponectin expression vary inversely with TNF-α and CRP [150-152]. Here the researchers [138] suggested post-translational changes in ADN since no direct effect of

etanercept was found on adipocyte ADN expression. Though, the authors suggest further studies to confirm this hypothesis, still the strengths of the study [138] lie in the study design, which involved double-blinding, conducting the study over a long-term period and indicating the significant therapeutic use of etanercept in future.

Study 10 [139] also assesses the effects of etanercept on obesity-induced inflammation and insulin resistance. Etanercept significantly improved adipose tissue-mediated inflammation through decreasing CRP levels and increasing the anti-inflammatory cytokine ADN in patients with metabolic syndrome. TNF-α is also known to stimulate IL-6 production by adipocytes in obese patients leading to further inflammation and etanercept was shown to cause a downward trend in IL-6 levels [139]. Though Study 10 [139] failed to show a relationship between etanercept treatment and improvement in insulin sensitivity in a greatly insulin-resistant obese sample of patients, the authors [139] attribute this to the short duration of the study or the moderate-sized sample of patients selected. As increased TNFR-2 levels were correlated with changes in CRP and ADN and it was concluded that it could be a marker for etanercept activity as a TNF-α inhibitor [139]. The strengths of this study [139], therefore, lie in the fact that it was a double-blinded study with a compliance of 100% since nurses in a clinical setting administered the treatment.

Since both the Studies 9 [138] and 10 [139] in Group III were unable to determine the exact effects of etanercept on insulin sensitivity, further studies need to be performed using gold standard clamp techniques to address this issue.

9. Conclusion

Group I studies [130-134] provide sufficient evidence of improved glycemic control post treatment with salsalates, which the authors attribute to decreased insulin clearance rather than a direct effect of salsalates on insulin secretion. These studies also provide evidence of reduced adipose tissue-induced inflammation after salsalate treatment and increased ADN levels, which further add to its anti-inflammatory and glycaemia-controlling effects in obese patients. Partially justifying the hypothesis, therefore, even though salsalates do not directly improve insulin sensitivity in obese patients, they can be a novel therapeutic approach for the management of glycaemia in obese patients by targeting the state of chronic inflammation that characterizes obesity.

Group II studies [135-137] more strongly confirm the hypothesis of a strong therapeutic agent, as TZD result in improved insulin sensitivity and also decrease obesity-induced inflammation by reducing adipocyte pro-inflammatory cytokine expression, adipose tissue macrophage content and immune cell infiltration into adipose tissue. These studies also establish a temporal link between decreased adipose tissue inflammation and improved insulin resistance.

Group III studies [138,139] confirm the utility of etanercept, another anti-inflammatory therapeutic agent, in improving glycemia and decreasing inflammation through reducing CRP and increasing ADN levels. But the hypothesis that insulin sensitivity can be improved by targeting the TNF-α pathway remains unsupported due to inconclusive results on the exact effects of etanercept on this parameter. Also, one of the side effects of etanercept is increased susceptibility to infection due to its anti-inflammatory effects, which could limit the use of etanercept in controlling obesity-induced insulin resistance [139].

Even with looking at only few studies analyzing each pathway, the hypothesis that targeting pro-inflammatory pathways in adipocytes with salicylates and TZD as a novel approache remains supported for reducing chronic inflammation-induced insulin resistance in obese patient with TZD emerging with the strongest effects.

In summary, while drugs that secondarily alter the inflammatory process are undoubtedly of great clinical importance, several lines of evidence suggest

that it might also be possible to directly target inflammation with pharmacological interventions to treat and/or prevent obesity induced insulin resistance, type 2 diabetes and metabolic syndrome. These approaches may provide more clinical benefits to a large number of affected persons.

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