RESEARCH PAPER

Effect of Dapagliflozin on Macrophages and its Impact in Obesity and Diabetes: An In Vitro Study

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ABSTRACT

Background: Obesity-associated adipose tissue inflammation is driven by resident immune cells of which macrophages are a key player. Adipose tissue macrophages (ATMs) contribute to insulin resistance and type 2 diabetes. Sodium–glucose cotransporter-2 (SGLT2) inhibitors such as dapagliflozin are one of the several classes of anti-diabetics commonly used in clinics. These have reported immunometabolic effects on macrophages. However, their impact on adipose-associated, metabolically activated macrophages (MMe) remains unclear.

Methods: THP-1 is a human derived monocytic cell line which is extensively used in biomedical research. These cells were stimulated with PMA and then polarized to M1 (LPS + IFN-γ), M2 (IL-4) or MMe (palmitate + high glucose + insulin) phenotypes. These sub-populations (THP-1, M1, M2, MMe) were treated with dapagliflozin (30 nM). RNA was extracted and gene expression of key markers were studied using qRT-PCR. Target transcripts included TNFα, IL-6, IL-1β, CD36, CD319 and CD209.

Results: Dapagliflozin produced a phenotype-dependent transcriptional response. In MMe all six targets were significantly modulated ($p < 0.05$). Similar but less extensive patterns were observed in THP-1 and M1 cells (notably strong upregulation of CD36, IL-1β and CD209 and downregulation of IL-6 in M1), while M2 cells showed modest changes (significant increases in CD36, IL-1β and CD209). The overall profile is consistent with a mixed metabolic–inflammatory (MMe-like) reprogramming resulting in increased lipid-handling (CD36) and inflammasome-linked cytokines (IL-1β, TNFα) coexisting with selective suppression of IL-6.

Conclusions: Dapagliflozin elicits a robust, phenotype-specific transcriptional reprogramming in THP-1–derived macrophages, most prominently in MMe cells. Rather than producing a simple anti-inflammatory (M1→M2) shift, dapagliflozin elicits a complex immunometabolic state characterized by enhanced lipid-handling and inflammasome-related signaling. These findings will have bearing on their clinical usage.

Keywords: Dapagliflozin, Adipose Tissue Macrophages (ATMs), Metabolically activated macrophage (MMe), Obesity, Type II diabetes, Immunometabolism

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INTRODUCTION

Obesity as a Global Pandemic

Obesity has become one of the major global health concerns of the 21st century, attaining epidemic levels in both developed and developing regions. Over 1 billion people are living with obesity as per estimates in 2022, representing nearly 13% of the world's population. The number of obese might increase to approximately 1.9 billion by 2035[1]. Since 1975, the prevalence of obesity has risen almost three fold, largely driven by rapid urbanization, reduced physical activity and a growing reliance on calorie-dense diets. Importantly, obesity is not merely a condition of excess adiposity but a multifactorial disease associated with a significantly increased risk of metabolic disorders, including type II diabetes mellitus, cardiovascular diseases and certain cancers[2].

Obesity and insulin resistance as inflammatory condition

Obesity is now widely recognized as a state of chronic low-grade systemic inflammation, often referred to as "metabolic inflammation," which plays a central role in the development of insulin resistance and associated metabolic complications[3]. Dysfunctional adipose tissue in obesity undergoes significant remodeling, characterized by hypertrophy, hypoxia, and infiltration of diverse immune cell populations, particularly adipose tissues macrophages (ATMs). In addition to ATMs, obese adipose tissue harbors increased numbers of **neutrophils, dendritic cells, mast cells, and adaptive immune cells such as $CD4^+$ Th1 cells, $CD8^+$ T cells and B cells**, all of which contribute to a pro-inflammatory milieu. Conversely, anti-inflammatory populations including **regulatory T cells (Tregs), Th2 cells, and eosinophils** are diminished or functionally impaired in obese adipose tissues, further skewing the immune balance toward inflammation[4].

This immune cell remodeling leads to increased secretion of cytokines such as TNF-α and IL-6, which leads to activation of Nuclear factor kappa B (NF-κB), suppressor of cytokine signaling (SOCS) proteins, cJun-N-terminal Kinase (JNK), Wingless-related integration site (Wnt), and Toll-like receptor (TLR) signaling pathways, ultimately impairing insulin signaling and glucose uptake in adipocytes and other peripheral tissues[5]. Furthermore, systemic inflammation serves as a critical mechanistic link between obesity and type II diabetes, as persistent cytokine signaling disrupts adipose tissue homeostasis and metabolic regulation[3]. The interplay between inflammation, macrophage activation, and other immune cell subsets underscores the immunometabolic nature of obesity and provides a strong rationale for targeting inflammatory pathways in therapeutic interventions.

Macrophages in Adipose Tissue as Key Players

ATMs are central mediators of the inflammation that links obesity to insulin resistance and type II diabetes. Early functional and *in vivo* studies demonstrated that diet-induced obesity drives recruitment and accumulation of distinct ATM subsets, particularly $F4/80^+CD11c^+/CD11b^+$ populations that localize to crown-like structures around dying adipocytes. They produce cytokines (TNF-α, IL-6) capable of impairing adipocyte insulin signalling and whole-body glucose homeostasis[6]. This phenotypic switch from an anti-inflammatory, tissue-remodelling state toward a proinflammatory ATM state was initially conceptualized within the framework of classical M1 and M2 polarization in obese and lean adipose tissue respectively[6].

However, the canonical M1/M2 binary classification does not fully capture ATM heterogeneity in metabolic disease. Further studies established a metabolically activated macrophage (MMe) cells, in obese conditions of high glucose, insulin and saturated fatty acids (e.g., palmitate), that are mechanistically and transcriptionally distinct from classical M1 activation. MMe macrophages are typified by upregulation of lipid-handling and metabolic markers such as **ABCA1, CD36, and PLIN2**, while exhibiting a hybrid inflammatory-metabolic phenotype that does not align strictly with M1 or M2 signatures[7]. These MMe markers correlate strongly with adiposity and reflect ATM adaptation to the lipid-rich, insulin-resistant adipose microenvironment. Complementary, recent *in vitro* work further recapitulates key MMe features like lipid accumulation, lysosomal stress and altered cytokine secretion, reinforcing that MMe macrophages represent the dominant, disease-relevant ATM phenotype in obesity and a more precise therapeutic target than the oversimplified M1/M2 paradigm[8]. **Given the central role of macrophages in metabolic inflammation, pharmacological agents that modulate macrophage function are of increasing therapeutic interest.**

Dapagliflozin and Its Immunometabolic Relevance

Dapagliflozin, a selective sodium–glucose cotransporter 2 (SGLT2) inhibitor, is an orally active antidiabetic agent that exerts its primary pharmacological action by inhibiting renal glucose reabsorption in the proximal tubules, thereby promoting glycosuria and reducing plasma glucose levels independent of insulin signaling[9]. By targeting SGLT2, which accounts for ~90% of renal glucose reabsorption, dapagliflozin not only improves glycemic control but also induces caloric loss, modest weight reduction, and osmotic diuresis, contributing to improved metabolic and cardiovascular outcomes[10].

Beyond glycemic effects, large-scale randomized controlled trial **DAPA-HF (**NCT03036124**)** has demonstrated that dapagliflozin significantly reduces hospitalization for heart failure and cardiovascular mortality, with benefits observed even in non-diabetic populations[10]. DELIVER (NCT03619213) expanded the indication to patients with heart failure and mildly reduced or preserved ejection fraction (HFpEF), showing reduction in CV death or worsening heart failure[11]. Mechanistically, these pleiotropic effects are attributed to

improvements in hemodynamic load, reduction in glucotoxicity, modulation of energy metabolism, and attenuation of inflammation and oxidative stress.

In patients with chronic kidney disease, in the DAPA-CKD (NCT03036150) randomized controlled trial, dapagliflozin significantly reduced the incidence of a composite renal outcome, including ≥50% decline in eGFR, end-stage kidney disease, or death from renal or cardiovascular causes[12]. The drug also demonstrated significant reductions in cardiovascular events and all-cause mortality. Importantly, these benefits were consistent across patients with and without type II diabetes, suggesting pleiotropic mechanisms beyond glycemic control.[12]

Despite its clinical benefits, dapagliflozin has faced regulatory scrutiny in certain regions due to safety concerns, particularly an increased risk of euglycemic diabetic ketoacidosis (DKA), genital infections and volume depletion. These risks led to initial hesitancy and restricted approvals in some countries, although it is not broadly "banned" but rather carefully regulated with specific contraindications and monitoring requirements. In UK dapagliflozin 5 mg is no longer authorized for the treatment of patients with type 1 diabetes mellitus[13]. In India, dapagliflozin is approved by the Central Drugs Standard Control Organization (CDSCO) and is widely prescribed for type 2 diabetes, heart failure and chronic kidney disease, both as monotherapy and in combination regimens, reflecting alignment with international guidelines. Its growing use in the Indian population is further supported by real-world evidence demonstrating efficacy in glycemic control and cardiorenal protection, making it a cornerstone of contemporary diabetes management strategies[14].

A systematic review shows that SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin) consistently suppress pro-inflammatory M1 programs and/or promote anti-inflammatory M2 features in multiple models by converging on several core pathways, notably inhibition of NF-κB and NLRP3, activation of AMPK (with downstream mTOR/autophagy effects), modulation of HMGB1–TLR signaling, and influences on STAT3 and PI3K/AKT signalling[15]. Thereby reducing IL-1β, IL-6, TNF-α and other cytokines and limiting macrophage infiltration and foam cell formation. In cardiovascular and renal models dapagliflozin/empagliflozin reduce macrophage infiltration and inflammatory signaling (with demonstrated benefits on atherosclerosis, HF and diabetic nephropathy), and in metabolic models empagliflozin and dapagliflozin have been reported to shift macrophage metabolism (e.g., reducing glycolysis via PFKFB3 inhibition, activating AMPK) and to alter polarization in liver and adipose contexts[15]. Important drug-specific nuances (e.g., stronger AMPK/autophagy signals for empagliflozin, STAT3 activation by dapagliflozin in cardiac models) and emphasize that most evidence is preclinical and mechanistic[15].

Knowledge Gap and Rationale

Existing literature is largely organ-level or uses circulating/peritoneal macrophages and does not provide deep, ATM-centric mechanistic data, especially for the **metabolically activated macrophage (MMe)** phenotype that predominates in obese adipose tissue. In other words, while SGLT2 inhibitors clearly modulate macrophage signaling and polarization in many contexts, **the specific actions of dapagliflozin on adipose-resident macrophages (ATMs), their MMe characteristics, lipid handling, lysosomal responses, and direct impact on adipose insulin resistance remain poorly characterized.** This study tries to fill this knowledge gap and bring some clarity on the direct effects of dapagliflozin on adipose-associated macrophages.

METHODOLOGY

Macrophage differentiation

THP-1 monocytes were maintained in RPMI-1640 supplemented with 10% fetal bovine serum and penicillin–streptomycin-neomycin at 37°C in a 5% CO_2 incubator. For differentiation, cells were plated at 5×10^5 cells per well in 6-well plates and treated with phorbol 12-myristate 13-acetate (PMA) at 5 ng·mL^{-1} for 24 h to generate adherent, resting macrophages (M0). M0 macrophages were then polarized as follows: M1 by stimulation with lipopolysaccharide (LPS, 50 ng·mL^{-1}) plus interferon-γ (IFN-γ, 20 ng·mL^{-1}); M2 by interleukin-4 (IL-4, 20 ng·mL^{-1}); and metabolically-activated macrophages (MMe) by combined exposure to palmitate (0.4 mM), high glucose (30 mM) and insulin (10 nM). All polarization treatments were applied for 24 h.

Cell Viability Assay

Cell viability was measured using CellTiter-Glo® Luminescent Kit (Promega) as per manufacturer's protocol. Briefly, 10,000 cells/well were seeded and differentiated in 96 well plate. Post differentiation cells were treated with dapagliflozin at different concentrations and further incubated for 24h. Post

incubation 100 µL/well CTG reagent was added. Plates were kept on shaker for 2 minutes and incubated in dark for 8 minutes. Luminescence was read in Varioskan plate reader. Vehicle treated wells were considered as 100% viability.

qRT-PCR

THP1, M1, M2 and MMe were treated with Dapagliflozin (30 nM) in triplicates and processed for downstream qRT-PCR assay (RNA isolation in TRIzol). Total RNA was extracted using a Krishgen RNA Fast PrepR-mini RNA isolation kit and 2 µg RNA was reverse-transcribed to cDNA. Gene expression was quantified with iTaq SYBR-green (Bio-Rad) qPCR using the 2^−ΔΔCt (Livak's method). Normalisation was done with β-actin housekeeping gene. Primer sequences were taken from earlier report[8].

Enzyme linked immunosorbent assay (ELISA)

TNF-α secretion was determined using Human TNF-α Quantikine ELISA kit (R&D SYSTEMS) as per manufacturer's protocol. Cells were seeded and differentiated in 6 well plate. Culture supernatant was used as sample. Test, standards and control samples were added to respective wells (50 µL per well) along with provided reagents. Plate was incubated at room temperature for 2 hours on a horizontal shaker. After washing, human TNF-α conjugate was added and further incubated for 2 hours at room temperature on the shaker. Plate was washed and 200 µL substrate solution was added in dark. After incubation for 30 minutes at room temperature the reaction was stopped by adding 50 µL of stop solution. The optical density was determined using a microplate reader set at 450 nm.

Statistical analysis

Student's t-test was used to determine differences in means (GraphPad Prism 10). Results were considered statistically significant when the p-value was less than 0.05.

RESULTS

We differentiated THP-1 cells into classically activated M1, alternatively activated M2 and metabolically activated MMe cells (Fig 1A) as described by Bhatia *et al.*[8]. Before treatment of these cells we performed cell viability assay on the different sub-populations of macrophages and found that the drug has no cytotoxic effect upto 100 µM (Fig 1B). We decided on a concentration of 30 nM of dapagliflozin which is well below the C_{max} (more than 5 fold) reported in human upon treatment with 5mg dose while being higher than the reported IC_{50} value for hSGLT2[16]. At this concentration the drug has no cytotoxicity in any of the cell types.

It is interesting to note that it produced a phenotype-dependent transcriptional response in different sub types of macrophages (summarized in Table 1).

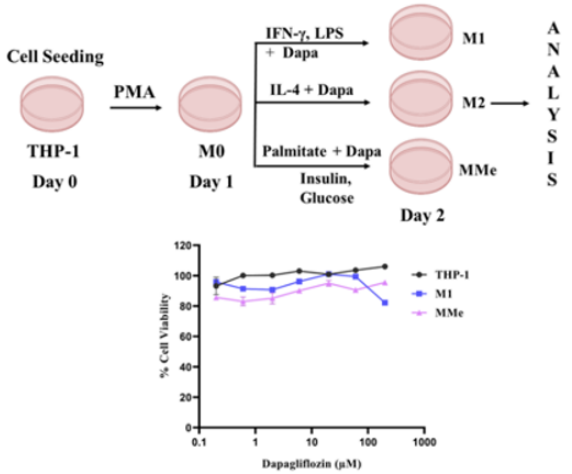

Figure 1: A) Schematic showing cell differentiation & treatment protocol, B) Effect of dapagliflozin on cell viability in different sub-types

Table 1: Relative Gene Expression After Dapagliflozin Treatment

Group	Gene	Fold change (treated/untreated)	SD	p value
THP-1	CD209	38.83	1.14	<0.001
THP-1	CD319	1.46	0.18	<0.001
THP-1	CD36	2.88	0.11	<0.001
THP-1	IL-1β	1.71	0.10	0.001
THP-1	IL-6	undetected	–	–
THP-1	TNFα	2.63	0.16	0.001
M1	CD209	25.65	0.65	<0.001
M1	CD319	0.55	0.03	<0.001
M1	CD36	1.58	0.01	<0.001

M1	IL-1β	1.59	0.09	0.002
M1	IL-6	0.73	0.03	0.002
M1	TNFα	1.27	0.20	0.088
M2	CD209	1.60	0.19	0.005
M2	CD319	0.82	0.20	0.243
M2	CD36	1.32	0.06	0.001
M2	IL-1β	1.16	0.05	0.008
M2	IL-6	1.17	0.10	0.577
M2	TNFα	0.93	0.07	0.753
MMe	CD209	165.54	11.82	<0.001
MMe	CD319	1.36	0.04	0.023
MMe	CD36	2.88	0.11	<0.001
MMe	IL-1β	1.93	0.16	0.001
MMe	IL-6	1.00	0.20	0.002
MMe	TNFα	1.67	0.12	0.001

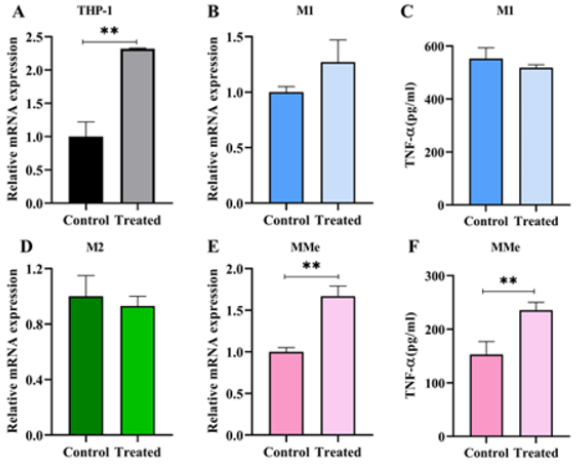

Figure 2: TNF-α upon treatment: relative gene expression (A, B, D and E) in THP-1, M1, M2, and MMe cells respectively. Protein quantification from media C, M1 and F, MMe cells using ELISA.

TNF-α is the most studied and documented cytokine with respect to adipose tissue inflammation and insulin resistance[3]. Dapagliflozin treatment increased the production of this cytokines in all macrophage subtypes except M2 (Fig 2), where it's expression is minimal. Most notable increase is in the MMe cells, indicating detrimental effects are enhanced under metabolic stimulation (Fig 2 E). We confirmed our findings by estimating the secreted TNF-α from the media of M1 (Fig 2C) and MMe cells (Fig 2F). While the baseline secretion of TNF-α is higher in M1 as reported earlier, dapagliflozin stimulates its secretion only in MMe cells. It is important to note that MMe cells are mostly found in obese adipose tissue and therefore dapagliflozin treatment may exacerbate insulin resistance by stimulating TNF-α secretion.

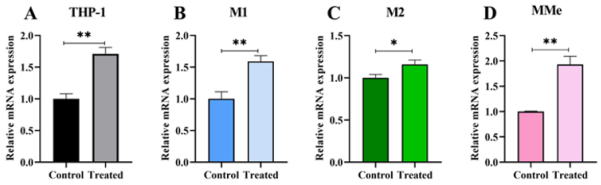

Figure 3: IL-1β relative gene expression upon dapagliflozin treatment in macrophage subtypes.

This increase is also seen in IL-1β which is elevated in both M1 and MMe macrophages to similar extent (Fig 3). Although IL-1β expression has gone up in all macrophage sub-population, it is important to remember that the absolute expression in THP-1 and M2 cells is negligible compared to MMe and M1 (its highest in M1)[8].

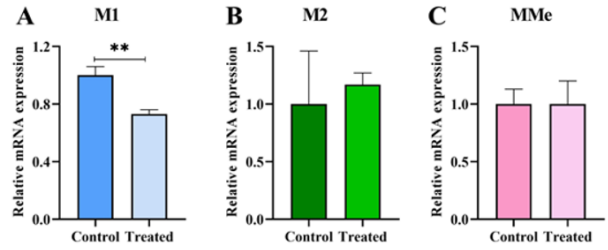

Figure 4: IL-6 relative gene expression upon dapagliflozin treatment in macrophage subtypes. IL-6 transcript was not detected in THP-1 cells.

Conversely, IL-6 expression decreased substantially in M1 and MMe macrophages (Fig 4). IL-6 is generally considered as an inflammatory cytokine but its role in insulin resistance and diabetes is not clear[3].

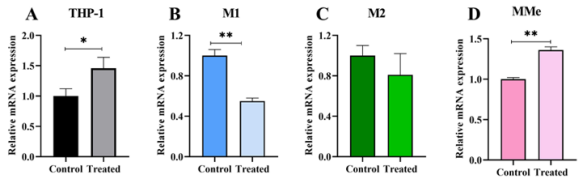

Figure 5: CD319 relative gene expression upon dapagliflozin treatment in macrophage subtypes.

Surface markers of M1 macrophages CD319 is one of the key regulators of chronic inflammation especially in TNF-α rich environments[17]. Dapagliflozin treatment reduced the expression of CD319 in the M1 macrophages, while increasing it in MMe cells (Fig 5). This increase is significant especially if seen in light with the greater increase in TNF-α in MMe cells. TNF-α work in an autocrine or paracrine fashion to increase the expression of CD319[17].

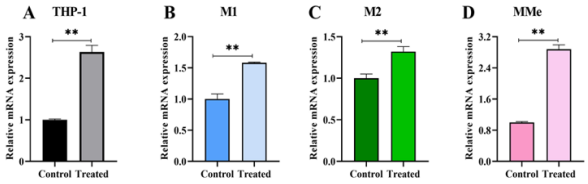

Figure 6: CD36 relative gene expression upon dapagliflozin treatment in macrophage subtypes.

CD36 is seen as a marker of MMe macrophages and its expression is higher in MMe compared to M2 or M1 cells[8]. It is a scavenger receptor which binds to oxidized LDL and also transports fatty acids. This CD36 expression is increased in all sub-populations of macrophages (Fig 6). Increased CD36 on macrophages is associated with increased cardiovascular risks while its deletion is known to be cardio protective and anti adipogenic[18].

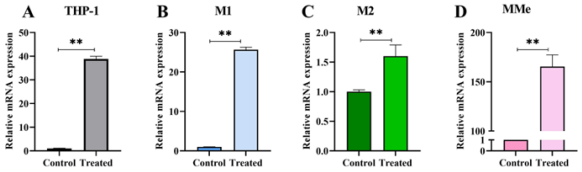

Figure 7: CD209 relative gene expression upon dapagliflozin treatment in macrophage subtypes.

CD206 is a lectin type scavenger receptor which is elevated in phagocytic macrophages. Within adipose tissue it is believed to be involved in clearing up necrotic or apoptotic adipocytes especially through M2 macrophages. Dapagliflozin increases its expression in all the sub-populations (Fig 7). However, considering its relative expression being substantially higher in M2 macrophages[8] its increase in other cells points to its role in increasing M2 macrophages. However, it is interesting to note that its expression has been found to be correlated with adipose tissue in severely obese individuals[19]. These data indicate dapagliflozin elicits a mixed metabolic–inflammatory program rather than a simple M1→M2 repolarization.

DISCUSSION

Macrophages within adipose tissue are a key driver of inflammation and insulin resistance. In a complex multifactorial disease like diabetes type 2, it is important to study each component separately for mechanistic insights. Here we have tried to address this by studying the effects of one of the key anti-diabetic dapagliflozin on adipose macrophages

Earlier report points out that dapagliflozin attenuates M1 polarization and reduces pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and apoptosis in murine peritoneal macrophages and LPS/IFNγ-stimulated THP-1 cells, via inhibition of the PI3K/AKT pathway (and effects are reversed by the PI3K agonist 740Y-P)[20]. In our human derived THP-1 model treated with **30 nM** dapagliflozin the transcriptional response is **phenotype-dependent and mixed. Reduced IL-6 is consistent with previous finding. However, increased TNF-α and IL-1β is contrary to the earlier finding[20]. These differences most likely reflect dose difference. While our nanomolar concentration is closer to steady human blood serum levels whereas earlier report used supraphysiological levels (100 µM)[20].**

Large CD209 fold change suggests that Dapagliflozin makes all macrophages more phagocytic[21]. This could be a beneficial change with respect to obesity because this means clearance of dead and necrotic adipocyte may be enhanced.

In literature CD36 is observed to facilitate a pro-inflammatory **paracrine loop** between adipocytes and macrophages; CD36 ligands (e.g., oxidized lipids) activate JNK and disrupt insulin signalling in both cell types[18]. CD36 knockout ($CD36^{-/-}$) mice on high-fat diets show **less adipose inflammation**, fewer crown-like structures, less JNK activation, improved insulin signalling (greater insulin-stimulated Akt phosphorylation) and improved glucose tolerance versus WT[18]. Given the CD36 deficiency protects mice from diet-induced adiposity, adipocyte cell death, macrophage/T-cell infiltration, and pro-inflammatory cytokine expression in WAT, and CD36 KO cells show reduced IL-6, TNF-α, MCP-1 and reduced apoptotic signalling[22], an increase in CD36 may be deleterious for obesity and insulin resistance. In adipocytes, it even

promotes fatty-acid uptake and triglyceride synthesis. In co-culture with macrophages it amplifies the inflammatory cross-talk[22]. Increase in CD36 along with increase in CD209 in MMe cells indicates possible increased clearance of dead adipocytes and augmented lysosomal activity[23]. The systematic reviews show SGLT2 inhibitors usually **suppress** some canonical pro-inflammatory outputs (IL-6, NLRP3, NF-κB) and in some contexts **reduce** M1 markers[15, 17]. Earlier studies generally did not focus on CD36 induction as a primary readout. Thus, CD36 upregulation via dapagliflozin is a **novel finding** relative to much of the reported SGLT2 literature and may reflect phenotype-specific effects in macrophages cells.

CONCLUSION

Our finding points to a more cautious approach in prescribing Dapagliflozin in type 2 diabetes owing to its complex effects especially with respect to inflammatory response, phagocytic activity and lipid processing abilities of macrophages within adipose tissue. The data may also partially explain the policy decisions by some nations to withhold its usage in clinic.

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Authors' contributions

Sandhya Tiwari and Sanjeev K Upadhyay conceptualized and designed the experiments. Sandhya Tiwari and Vikas Kumar Gupta performed all the experiments and interpreted the data. The first draft of the manuscript was written by Aryan Shukla. Sanjeev K Upadhyay secured the grant, and edited and finalized the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicts of Interests

Author declares that they have no conflict of interest.

Ethics approval and consent to participate

Not applicable as no experiment was conducted on any animal or human.

Availability of data and materials

Not Applicable. The authors confirm that the data supporting the findings of this study are available within the article.

Use of Artificial Intelligence

Not applicable

Declarations

Authors declare that all work is original and this manuscript has not been published in any other journal.

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