Farabi Tıp Dergisi 4(3):80-87,2025
Farabi Medical Journal 4(3):80-87,2025
https://doi.org/10.59518/farabimedj.1702978

FARABİ TIP DERGİSİ
FARABI MEDICAL JOURNAL

Özgün Makale
Original Article

https://dergipark.org.tr/tr/pub/farabimedj

The Effect of Topiramate on Adiponectin Secretion in 3T3-L1 Adipocytes: An *In Vitro* Approach to Anti-Obesity Mechanisms

Topiramatın 3T3-L1 Hücrelerinde Adiponektin Salınımı Üzerine Etkisi: Anti-obezite Mekanizmalarına Yönelik Bir *İn Vitro* Yaklaşım

Aysegul Sumer[1,a,*]

[1]*Recep Tayyip Erdogan University, Faculty of Medicine, Department of Medical Biocehmistry, Rize, Türkiye.*

**Corresponding author e-mail*: *aysegul.sumer@erdogan.edu.tr*

[a]*https://orcid.org/0000-0003-4918-4368*

ABSTRACT

This study aimed to investigate the effects of topiramate, a pharmacological agent with emerging metabolic benefits on adipocyte differentiation and adipokine secretion, with a particular focus on adiponectin levels in 3T3-L1 adipocytes. 3T3-L1 preadipocytes were induced to differentiate and subsequently treated with varying concentrations of topiramate (1–100 µM). Lipid accumulation was evaluated using Oil Red O staining, while adiponectin levels were measured via ELISA at 6, 12, and 24 hours. Cell viability was assessed using the MTT assay. Topiramate promoted significant lipid accumulation without cytotoxicity at concentrations up to 100 µM, with the 50 µM dose showing the highest lipid deposition. A significant increase in adiponectin secretion was observed in differentiated cells at 12 and 24 hours post-treatment ($p<0.01$), with the highest levels detected at 24 hours ($p<0.001$). Topiramate enhances adipocyte maturation and stimulates adiponectin secretion, indicating potential insulin-sensitizing and anti-inflammatory effects. These findings suggest that topiramate may exert part of its anti-obesity effects through adiponectin-mediated mechanisms and highlight its potential as a therapeutic agent in metabolic disease management.

Keywords: Adipogenesis, Adiponectin, Obesity, Topiramate, 3T3-L1 cells

ÖZET

Bu çalışma, metabolik açıdan giderek daha fazla yararları ortaya çıkan farmakolojik bir ajan olan topiramatın adiposit farklılaşması ve adipokin salınımı üzerindeki etkilerini, özellikle 3T3-L1 adipositlerinde adiponektin düzeylerine odaklanarak araştırmayı amaçlamıştır. 3T3-L1 preadipositleri farklılaşmaya indüklenmiş ve ardından değişen konsantrasyonlarda (1–100 µM) topiramat ile muamele edilmiştir. Lipit birikimi, Oil Red O boyama yöntemi kullanılarak değerlendirilmiş; adiponektin düzeyleri ise 6, 12 ve 24. saatlerde ELISA ile ölçülmüştür. Hücre canlılığı MTT testi ile belirlenmiştir. Topiramat, 100 µM'a kadar olan konsantrasyonlarda sitotoksisite oluşturmadan anlamlı lipit birikimi sağlamış, en yüksek lipit depolanması 50 µM dozunda gözlenmiştir. Farklılaşmış hücrelerde, tedaviden sonraki 12. ve 24. saatlerde adiponektin salınımında anlamlı bir artış saptanmış ($p<0.01$) ve en yüksek düzeyler 24. saatte belirlenmiştir ($p<0.001$). Topiramat, adiposit olgunlaşmasını artırmakta ve adiponektin salınımını uyarmaktadır; bu da potansiyel insülin-duyarlılaştırıcı ve antiinflamatuvar etkilerine işaret etmektedir. Bulgular, topiramatın kilo düşürücü etkilerinin bir kısmını adiponektin aracılı mekanizmalar üzerinden gösterebileceğini ve metabolik hastalıkların tedavisinde potansiyel bir ajan olabileceğini ortaya koymaktadır.

Anahtar Kelimeler: Adipogenez, Adiponektin, Obezite, Topiramat, 3T3-L1 hücreleri

Geliş Tarihi/Received Date: 20.05.2025 | *Kabul Tarihi/Accepted Date: 01.09.2025*

INTRODUCTION

Obesity is a multifactorial chronic disease that has reached epidemic proportions globally and poses a significant threat to public health. It is associated with an increased risk of numerous comorbidities, including type 2 diabetes mellitus, cardiovascular diseases, non-alcoholic fatty liver disease, and several forms of cancer.[1] The pathophysiology of obesity is complex and involves genetic, environmental, and behavioral factors that lead to an imbalance between caloric intake and energy expenditure. Importantly, obesity is characterized not only by an excess accumulation of adipose tissue but also by profound alterations in the endocrine and immune functions of this tissue.[2]

Adipose tissue, once considered an inert depot for energy storage, is now recognized as a highly dynamic and metabolically active organ that plays a central role in maintaining energy homeostasis. It is composed of various cell types, including adipocytes, preadipocytes, macrophages, and endothelial cells, all of which contribute to its endocrine function.[3] In obesity, adipose tissue undergoes significant remodeling, including adipocyte hypertrophy, increased infiltration of immune cells, and altered secretion of signaling molecules. These changes impair the normal metabolic and endocrine functions of adipose tissue and contribute to systemic insulin resistance and chronic low-grade inflammation.[4]

One of the hallmark features of adipose tissue dysfunction in obesity is the dysregulated secretion of adipokines bioactive peptides and proteins released by adipocytes that act in autocrine, paracrine, and endocrine manners to influence systemic metabolism.[5] Adipokines such as leptin, resistin, visfatin, and adiponectin play key roles in regulating appetite, glucose metabolism, lipid homeostasis, and immune responses. In the obese state, the balance of pro-inflammatory and anti-inflammatory adipokines is disrupted, tipping toward a pro-inflammatory milieu that promotes insulin resistance and metabolic complications.[6]

Adiponectin is a unique adipokine that stands out for its anti-inflammatory, insulin-sensitizing, and anti-atherogenic properties. Unlike most adipokines, adiponectin levels are paradoxically decreased in obesity, with low circulating concentrations correlating with increased risk of metabolic syndrome, type 2 diabetes, and cardiovascular disease.[7] Adiponectin exerts its effects through AdipoR1 and AdipoR2 receptors, activating downstream signaling pathways such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-alpha (PPAR-α), which enhance fatty acid oxidation and improve insulin sensitivity.[8] Thus, therapeutic strategies aimed at increasing adiponectin levels or enhancing its signaling have garnered interest in the context of metabolic disease management.

Topiramate, a sulfamate-substituted monosaccharide initially approved as an anticonvulsant, has gained attention in recent years for its weight-reducing and metabolic regulatory effects. Clinical studies have demonstrated that topiramate induces significant weight loss in obese patients, especially when used in combination with other agents such as phentermine.[9,10] Although the precise mechanisms remain to be fully elucidated, topiramate is believed to suppress appetite, modulate neurotransmitter activity, and potentially alter energy metabolism. Emerging data suggest that topiramate may also exert effects on adipose tissue biology and adipokine secretion, including the modulation of adiponectin levels, thereby contributing to its overall metabolic benefits.[11] However, the precise molecular mechanisms underlying these effects especially in relation to adipokine regulation remain insufficiently characterized.

Given adiponectin's pivotal role in metabolic homeostasis and the observed reduction of its levels in obesity, there is growing interest in pharmacological agents that can enhance its expression and signaling. Topiramate, due to its favorable metabolic profile, represents a promising candidate in this context. Nonetheless, further research is needed to clarify how topiramate affects adiponectin production and function at the cellular level. To address this knowledge gap, the present study aimed to investigate the effects of topiramate on adiponectin expression using 3T3-L1 cells, a well-established murine preadipocyte model widely employed to study adipocyte differentiation and adipokine dynamics. Given their capacity to recapitulate key features of adipogenesis and adipokine secretion, 3T3-L1 cells provide a robust *in vitro* platform to evaluate the potential of pharmacological agents to modulate adipocyte function.

METHODS

Ethical approval

This study does not require ethical approval as it is a computational study.

Chemicals

Topiramate, Sigma, T0575-10MG Biotin, [3-(4,5-dimethylthiazol-2-yl)]-2,5-diphenyltetrazolium bromide (MTT), and Oil Red O were purchased from Sigma-Aldrich (St. Louis, MO, USA). Fetal bovine serum (FBS) was obtained from Biochrom (Berlin, Germany). Dulbecco's Modified Eagle's Medium (DMEM) was acquired from the American Type Culture Collection (ATCC, Manassas, VA, USA). 2-Propanol was purchased from J.T. Baker (PA, USA). Mouse adiponectin levels were measured using a commercial ELISA kit (Mouse Adiponectin ELISA Kit, Cat. No: EMA2500-1, Lot No: 071041003; AssayPro, St. Charles, MO, USA).

Cell culture and differentiation protocol

3T3-L1 preadipocytes (ATCC, Manassas, VA, USA) were cultured in Dulbecco's Modified Eagle's Medium (DMEM; ATCC) supplemented with 10% fetal bovine serum (FBS; Biochrom, Berlin, Germany) under standard conditions (37 °C, 5% CO_2, humidified atmosphere). For adipogenic differentiation, cells were seeded in 6-well plates and allowed to reach full confluence. Two days post-confluence (designated day 0), the medium was replaced with an induction cocktail containing DMEM, 10 µg/mL insulin, 0.25 µM dexamethasone, 0.5 mM IBMX, and 100 ng/mL biotin (Sigma-Aldrich, St. Louis, MO, USA), and incubated for four days.[12]

On day 4, cells were switched to maintenance medium (DMEM with 10% FBS, 10 µg/mL insulin) containing various concentrations of topiramate (TPM). TPM was dissolved in DMEM and diluted to final concentrations; control groups received vehicle (DMEM) only. On day 6, the medium was refreshed with DMEM supplemented with 10% FBS, 10 µg/mL insulin, and 100 ng/mL biotin to promote further maturation. Treatments were maintained consistently to evaluate TPM's effects on adipogenic differentiation.

Oil red O staining

Lipid accumulation in differentiated adipocytes was assessed by Oil Red O staining, following the method of Ramírez-Zacarías et al.[13] with minor modifications. Cells were washed twice with phosphate-buffered saline (PBS) and fixed with 10% neutral-buffered formalin for 1 hour at room temperature. After fixation, wells were rinsed twice with 60% 2-propanol to prepare for staining.

Cells were then incubated with freshly prepared Oil Red O working solution for 10 minutes at room temperature. Excess stains were removed by washing the wells five times with distilled water. Lipid droplets were visualized and imaged using an inverted phase-contrast microscope (Nikon Eclipse TS100, Tokyo, Japan).

For quantification, 100% 2-propanol was added to elute the retained dye, and a 1 mL aliquot of the eluate from each well was collected. Absorbance was measured at 520 nm using a UV-visible spectrophotometer (Shimadzu UV1601, Kyoto, Japan). Absorbance values were used to quantify intracellular lipid accumulation.

Cell viability assay

Cell viability was evaluated using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay, as originally described by Mosmann.[14] Briefly, 3T3-L1 cells were seeded into flat-bottom 96-well plates and allowed to adhere for 24 hours. After attachment, the cells were treated with various concentrations of topiramate (TPM; µM; 0, 1, 5, 10, 25, 50, 100, 250, 500, 750, 1000) and incubated for 72 hours under standard culture conditions.

MTT solution (final concentration: 0.25 mg/mL) was added to each well and cells were incubated for 4 hours at 37°C. During this incubation period, viable cells reduce MTT to purple formazan crystals via mitochondrial dehydrogenase enzymes. Following incubation, the medium was removed, and formazan crystals were solubilized in 100 µL of DMSO per well to allow quantification. Absorbance was measured at 570 nm using a microplate reader (Versamax, Molecular Devices, CA, USA).

The optical density (OD) values were used to calculate cell viability as a percentage of the untreated control group using the following formula:[15] Cell viability (%) = $OD_{treatment}/OD_{control} \times 100$

Adiponectin measurement

To evaluate the effect of topiramate on adiponectin secretion, fully differentiated 3T3-L1 adipocytes were first washed with PBS, and the culture medium was replaced with serum-free Dulbecco's Modified Eagle's Medium (DMEM). Cells were then treated with topiramate, and culture supernatants were collected at 6, 12 and 24 hour post-treatment.

The selection of 6, 12 and 24 hour time points for collecting culture supernatants was based on standard time-course protocols commonly used in secretory response assays of adipocytes. These intervals were chosen to capture both early (6 h) and intermediate (12 h) stages of adiponectin secretion, as well as the later or sustained phase (24 h) following topiramate treatment.

Adiponectin secretion is known to be a dynamic process regulated by intracellular signaling cascades and transcriptional events, which can respond to pharmacological stimuli over varying time frames. Early changes (within a few hours) may reflect rapid post-translational or signaling effects, while later time points can indicate transcriptional regulation or accumulated secretion. Therefore, this time-course design allows for a comprehensive evaluation of both acute and delayed effects of topiramate on adiponectin release from mature adipocytes.

Adiponectin levels in the collected supernatants were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions (Assay Pro Mouse Adiponectin ELISA Kit, Cat. No: EMA2500-1, Lot No: 071041003). Quantification was carried out using a standard curve generated from known concentrations of recombinant adiponectin, and the results were expressed as nanograms per milliliter (ng/mL).

Statistical analysis

To compare the levels of differentiation among the experimental groups, one-way analysis of variance (One-Way ANOVA) was performed. When the ANOVA indicated a statistically significant difference, Tukey's Honestly Significant Difference (HSD) post-hoc test was conducted to determine which specific group comparisons accounted for the observed differences. Additionally, to examine the relationship between differentiation level and the adiponectin levels, Spearman's rho correlation analysis was performed, taking into consideration the distribution characteristics of the variables. A significant level of $p<0.05$ was adopted for all analyses. Statistical analyses were conducted using SPSS software, version 23.0.

RESULTS

Effect of topiramate on the viability of 3T3-L1 cells

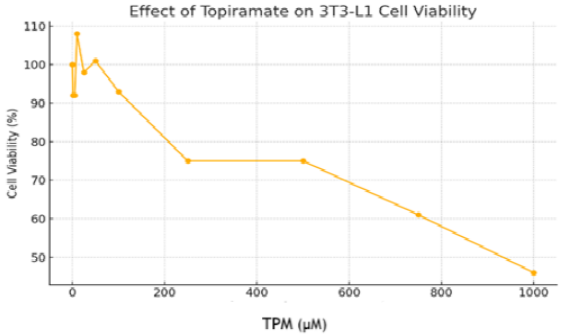

Figure 1. Effect of topiramate on the viability of 3T3-L1 adipocytes as determined by MTT assay

The cytotoxic effect of topiramate on 3T3-L1 cells was assessed using the MTT assay. Cells were treated with increasing concentrations of topiramate (1–1000 µM) for 72 hours, and cell viability was calculated relative to the untreated control group (Figure 1). The results revealed that topiramate exhibited no significant cytotoxic effect at lower concentrations (1–100 µM), with cell viability remaining above 90% in these groups. However, a marked decline in cell viability was observed at 250 µM and 500 µM concentrations. At 250 µM, cell viability dropped to approximately 65%, while treatment with 500 µM further reduced viability to nearly 40%. This concentration-dependent decrease in viability suggests that topiramate may exert cytotoxic effects at higher doses. These findings support the selection of the 1–100 µM concentration range as non-cytotoxic and physiologically relevant for subsequent experiments, including differentiation and adipokine analysis. The absence of cytotoxicity at these doses also reinforces the reliability of downstream functional assays involving topiramate treatment.

Effect of topiramate on adipogenic differentiation of 3T3-L1 cells

The effect of topiramate on adipogenic differentiation of 3T3-L1 cells was assessed using the Oil Red O staining method, a widely accepted technique for evaluating intracellular lipid accumulation. Lipid accumulation was quantified by measuring the absorbance of the extracted Oil Red O dye at 520 nm using a spectrophotometer (Table 1).

Table 1. Effect of topiramate on adipogenic differentiation of 3T3-L1 cells

	$\bar{X}$	SD	F	p	Tukey
B (Undiff)[a]	0.38	0.01			a<b,c,d,e,f,g
0 (Diff)[b]	0.52	0.01			b<f,g
1µM[c]	0.53	0.02			c< f,g
5µM[d]	0.52	0.01	15.6	**0.000***	d<f,g
10µM[e]	0.54	0.01			e<f,g
50µM[f]	0.63	0.01			f>a,b,c,d,e,g
100µm[g]	0.59	0.01			g>a,b,c,d,e g<f

One-way ANOVA revealed a statistically significant difference in differentiation levels among the cell groups ($F_{(6,14)}=158.603$; $p<0.001$). To identify the specific group differences contributing to this significance, pairwise comparisons were conducted using Tukey's post hoc test.
a; B (undifferentiated), b; 0 (Differentiated), c; 1 µM, d; 5 µM, e; 10 µM, f; 50 µM, g; 100 µM.
F; One-Way ANOVA, $p<0.05$, $\bar{X}$; Mean, SD; Standart Deviation

The undifferentiated cells exhibited significantly lower levels of differentiation compared to all other groups ($p<0.05$). In contrast, the 50 µM group showed the highest differentiation levels among all groups, with statistically significant differences ($p<0.05$). The 100 µM group demonstrated significantly higher differentiation compared to the differentiated with no TPM 0, 1 µM, 5 µM, and 10 µM groups ($p<0.05$), but significantly lower differentiation than the 50 µM group ($p<0.05$). These findings indicate a pronounced and dose-dependent effect of different treatment conditions on adipogenic differentiation.

According to the Tukey HSD post hoc analysis, a statistically significant difference was observed between undifferentiated cells and the 0 group ($p<0.001$). The mean differentiation value of the undifferentiated group ($\bar{X}=0.38$) was significantly lower than that of the 0 group ($\bar{X}=0.52$). Furthermore, the undifferentiated group also exhibited significantly lower differentiation levels compared to the 1 µM, 5 µM, 10 µM, 50 µM, and 100 µM groups ($p<0.05$). The 0 group, on the other hand, showed significantly lower differentiation than the 50 µM and 100 µM groups ($p<0.05$), but did not differ significantly from the 1 µM, 5 µM, and 10 µM groups ($p>0.05$). These results indicate that topiramate promotes lipid accumulation in a dose-dependent manner, potentially by enhancing adipocyte differentiation or lipid uptake pathways.

Effects of topiramate on adiponectin levels

To investigate whether topiramate modulates adiponectin secretion as an indicator of its potential role in adipocyte differentiation, fully differentiated 3T3-L1 adipocytes were treated with topiramate, and the levels of adiponectin secreted into the culture supernatants were measured using a quantitative ELISA. This approach allowed for the assessment of topiramate's effect on the functional output of mature adipocytes, as adiponectin is a key adipokine associated with adipocyte maturation and metabolic activity.

Adiponectin levels were assessed at 6, 12, and 24 hours. A significant increase in adiponectin concentration was observed in differentiated cells compared to undifferentiated controls at 12 and 24 hours ($P<0.01$). Furthermore, at 24 hours, adiponectin levels were significantly higher across all concentrations compared to both 6- and 12-hour time points ($P<0.001$) (Figure 2). These results support the hypothesis that topiramate enhances adipogenic differentiation, as differentiated cells are expected to secrete higher levels of adipokines such as adiponectin.

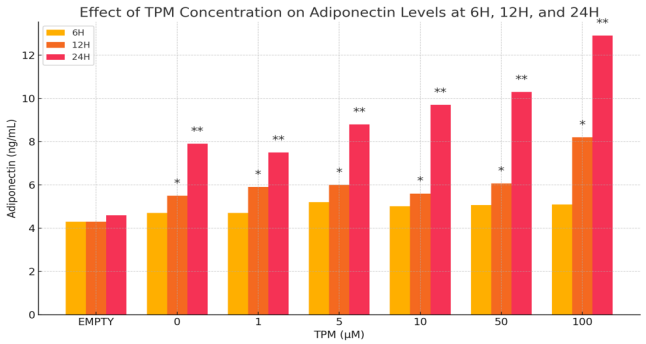

Figure 2. Changes in adiponectin levels over time and across topiramate concentrations in differentiated cells
(*P<0.01 compared to undifferentiated cells; **P<0.001 compared to 6- and 12-hour time points)

Correlation between adiponectin levels and lipid accumulation

Spearman's rank correlation analysis was performed between adiponectin levels and intracellular lipid accumulation, as assessed by Oil Red O staining. The analysis demonstrated a moderate positive correlation ($\rho=0.464$), but this relationship was not statistically significant ($p=0.294$). Although the result does not reach statistical significance, the trend suggests a potential link between adiponectin secretion and lipid accumulation during differentiation.

DISCUSSION

Beyond serving as a passive lipid storage depot, adipose tissue is an active endocrine organ that secretes a wide range of bioactive molecules, adipokines that modulate metabolic homeostasis, inflammation, and insulin sensitivity.[1] Among these, adiponectin is of particular interest due to its insulin-sensitizing, anti-inflammatory, and anti-atherogenic properties.[17] In obesity, circulating adiponectin levels are paradoxically reduced despite increased adiposity, contributing to the pathogenesis of insulin resistance and metabolic syndrome.[18] Restoration of adiponectin levels is therefore a potential therapeutic target in obesity management.[19] Topiramate has been primarily used as an antiepileptic and antimigraine agent; however, its weight-reducing and insulin-sensitizing effects have garnered increasing attention in metabolic research. Although the mechanisms are not yet fully elucidated, studies suggest that topiramate modulates central appetite regulation, increases thermogenesis, and improves glucose and lipid metabolism. Importantly, recent data indicate that

topiramate may influence adipose tissue remodeling and adipokine secretion.[20-22]

In the present study, Oil Red O staining was used to evaluate intracellular lipid accumulation as an indicator of adipogenic differentiation in 3T3-L1 adipocytes. Quantitative analysis revealed that topiramate increased lipid accumulation in a dose-dependent manner within the non-cytotoxic concentration range (1–100 μM). The most pronounced effect was observed at 50 μM, where lipid deposition was significantly higher compared to both untreated differentiated controls and lower drug concentrations, indicating an optimal dose for promoting adipogenesis under these experimental conditions. At supraphysiological doses (≥250 μM), lipid accumulation markedly declined, which aligns with the observed reduction in cell viability, indicating cytotoxicity-mediated suppression of differentiation. From a mechanistic perspective, enhanced lipid accumulation in mature adipocytes is typically interpreted as an indicator of effective differentiation, which in turn is often associated with improved adipokine secretion profiles, particularly adiponectin. In obesity, impaired adipogenesis and the predominance of hypertrophic, dysfunctional adipocytes contribute to reduced adiponectin production, increased pro-inflammatory cytokine release, and systemic insulin resistance. Pharmacological agents that promote the formation of smaller, metabolically active adipocytes can restore endocrine function and ameliorate metabolic derangements.[16,17,20] Interestingly, the positive relationship observed between lipid accumulation and adiponectin secretion in our study, although not statistically significant, suggests that topiramate may enhance adipocyte maturation in parallel with endocrine competence. The 50 μM concentration may therefore represent a threshold where topiramate optimally supports both lipid storage capacity and beneficial adipokine output without inducing lipotoxicity. It is important to note that in the context of obesity therapy, increased lipid accumulation within adipocytes *in vitro* does not necessarily translate to adverse effects *in vivo*. On the contrary, healthy adipogenesis can facilitate the safe sequestration of fatty acids into subcutaneous depots, thereby reducing ectopic fat deposition in liver and muscle and improving whole-body insulin sensitivity.[23,24] In this light, the Oil Red O findings of our study support the hypothesis that topiramate may improve adipose tissue health not by reducing the number of adipocytes, but by enhancing their functional capacity. Future studies should investigate whether the increased lipid accumulation observed here is accompanied by changes in lipogenic and lipolytic gene expression (e.g., PPARγ, C/EBPα, ATGL, HSL) and whether similar effects are seen in primary human adipocytes. Such analyses would clarify whether topiramate's effect on adipogenesis is mediated through canonical differentiation pathways.

In this study, adiponectin secretion in 3T3-L1 adipocytes increased significantly following topiramate treatment, with the most pronounced elevations observed at 12 and 24 hours across all non-cytotoxic concentrations (1–100 μM). This time-dependent increase suggests that topiramate exerts both early and sustained stimulatory effects on adiponectin production. The delayed peak at 24 hours may reflect transcriptional upregulation, protein synthesis, and secretion processes, consistent with the known kinetics of adipokine regulation in mature adipocytes.[16,17,25] The correlation analysis revealed a moderate but non-significant positive relationship between lipid accumulation and adiponectin secretion ($\rho=0.464$, $p=0.294$). Although not statistically significant, the direction of this association is biologically plausible. Well-differentiated, metabolically healthy adipocytes generally store more triglycerides and produce higher levels of adiponectin. The lack of statistical significance here may be due to the limited sample size or intrinsic variability in *in vitro* adipokine measurements. Nevertheless, the trend suggests that topiramate's promotion of adipogenesis (as indicated by Oil Red O staining) and its enhancement of adiponectin secretion may be mechanistically linked. Clinically, this dual effect is relevant because healthy adipose tissue expansion coupled with increased adiponectin can help divert lipids away from ectopic sites such as liver and muscle, thereby mitigating lipotoxicity and improving whole-body metabolic homeostasis.[26] Moreover, adiponectin elevation could partially explain the metabolic improvements observed in clinical trials of topiramate-containing weight-loss regimens.

Topiramate is clinically recognized for its weight-reducing effects, particularly when combined with phentermine, primarily attributed to appetite suppression and reduced caloric intake.[21] However, our findings suggest that direct modulation of adipocyte function enhancing differentiation and adiponectin secretion may represent an additional peripheral mechanism. This dual action could provide synergistic

benefits in obesity management, addressing both energy intake and adipose tissue health. Given that low adiponectin levels in obesity are associated with insulin resistance, type 2 diabetes, and cardiovascular disease, pharmacologically induced increases in adiponectin especially in parallel with improved adipogenesis may translate into meaningful metabolic improvements.[27,28]

Beyond its impact on adiponectin regulation, topiramate may exert additional metabolic benefits through other mechanisms. Experimental and clinical studies have reported that topiramate can reduce oxidative stress by enhancing antioxidant defense systems and lowering reactive oxygen species production. Furthermore, topiramate has been shown to improve mitochondrial function, potentially through modulation of mitochondrial biogenesis and efficiency, which could contribute to improved cellular energy homeostasis.[29]

Although our findings suggest a potential metabolic benefit of topiramate reflected by increased adiponectin secretion no direct measurements of insulin sensitivity were performed in this study. Key indicators such as GLUT4 expression, glucose uptake assays, or phosphorylation levels of insulin signaling intermediates (e.g., Akt or IRS-1) were not assessed. Therefore, any inference regarding improved insulin sensitivity remains speculative. Given the well-established role of adiponectin in enhancing insulin responsiveness, it is reasonable to hypothesize that the observed increase in adiponectin may contribute to such effects. However, this interpretation should be made cautiously. Future studies should include specific molecular and functional analyses to determine whether topiramate indeed improves insulin signaling pathways in adipocytes. A more appropriate conclusion, given the current data, would be: "Since adiponectin is associated with improved insulin sensitivity, this possibility should be explored in future studies".

The strength of this study lies in its integrated assessment of adipogenesis, adiponectin secretion, and cytotoxicity across a concentration range, allowing identification of an optimal effective dose (50 µM) for *in vitro* adipocyte function. However, the *in vitro* model does not capture systemic influences such as neural regulation, hepatic lipid metabolism, or long-term tissue remodeling. Additionally, total adiponectin was measured without distinguishing high-molecular-weight (HMW) forms, which possess the strongest metabolic effects. Future studies should assess the expression of adipogenesis-related transcription factors such as PPARγ and C/EBPα, as well as lipid metabolism genes including ATGL and HSL, to clarify the molecular basis of the observed effects. In addition, incorporating inflammatory marker profiling would help determine whether topiramate exerts anti-inflammatory actions alongside its metabolic effects. Finally, validating these findings in primary human adipocytes and *in vivo* models with comprehensive metabolic readouts will be essential to confirm their translational relevance.

CONCLUSION

In conclusion, this study provides novel evidence that topiramate enhances adipogenesis and adiponectin secretion in 3T3-L1 adipocytes at non-cytotoxic doses, with optimal effects at 50 µM. These findings suggest that topiramate's anti-obesity action may extend beyond appetite suppression to include direct improvement of adipose tissue endocrine function, potentially contributing to enhanced insulin sensitivity and reduced inflammation. By promoting the development of metabolically healthy adipocytes and restoring a favorable adipokine profile, topiramate may offer a multifaceted approach to obesity treatment.

Authorship contribution statement

Consept and desing: AS.
Acquisition of data: AS.
Analysis and interpretation of data: AS.
Drafting of the manuscript: AS.
Critical revision of the manuscript for important intellectual content: AS.
Statistical analysis: AS.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

This study does not require ethical approval as it is a computational study.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

No financial support was received for this research.

REFERENCES

1. Abad-Jiménez Z, Vezza T. Obesity: a global health challenge demanding urgent action. Biomedicines. 2025;13(2):502.
2. Kirichenko TV, Markina YV, Bogatyreva AI, Tolstik TV, Varaeva YR, Starodubova AV. The role of adipokines in inflammatory mechanisms of obesity. Int J Mol Sci. 2022;23(23):14982.

3. Jia Y, Lacombe M, Muller C, Milhas D. Adipose tissue and androgens: the ins and outs. Adipocyte. 2025;14(1):2508885.
4. Song Q, Xu P, Xiao Q, Zhang C, Mao Y. Crosstalk between white adipose tissue and skin: unraveling its role in psoriasis pathogenesis. Mol Med Rep. 2025;31(6):169.
5. Kushner RF, Shapiro M. Obesity: assessment and treatment across the care continuum. Ann Med. 2025;57(1):2521433.
6. Almpanidou S, Vachliotis ID, Goulas A, Polyzos SA. The potential role of adipokines and hepatokines in age-related ocular diseases. Metab Open. 2025;26:100365.
7. Supriya R, Tam BT, Yu AP, et al. Adipokines demonstrate the interacting influence of central obesity with other cardiometabolic risk factors of metabolic syndrome in Hong Kong Chinese adults. PLoS One. 2018;13(8):e0201585.
8. Lee S, Kwak HB. Role of adiponectin in metabolic and cardiovascular disease. J Exerc Rehabil. 2014;10(2):54-59.
9. Kulkarni C, Kumar S, Khatoon S, et al. Isovitexin, a natural adiponectin agonist, prevents glucocorticoid-induced osteosarcopenia. Endocrine. 2025;89(2):565-577.
10. Xiong GL, Gadde KM. Combination phentermine/topiramate for obesity treatment in primary care: a review. Postgrad Med. 2014;126(2):110-116.
11. De Simone G, Supuran CT. Antiobesity carbonic anhydrase inhibitors. Curr Top Med Chem. 2007;7(9):879-884.
12. Mentese A, Alver A, Sumer A, Demir S. Effects of homocysteine on adipocyte differentiation and CD36 gene expression in 3T3-L1 adipocytes. J Cell Commun Signal. 2016;10(1):55-60.
13. Ramírez-Zacarías JL, Castro-Muñozledo F, Kuri-Harcuch W. Quantitation of adipose conversion and triglycerides by staining intracytoplasmic lipids with Oil Red O. Histochemistry. 1992;97(6):493-497.
14. Mosmann T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J Immunol Methods. 1983;65(1-2):55-63.
15. Xuan H, Li Z, Yan H, et al. Antitumor activity of Chinese propolis in human breast cancer MCF-7 and MDA-MB-231 cells. Evid Based Complement Alternat Med. 2014;2014:280120.
16. Baldelli S, Aiello G, Mansilla Di Martino E, et al. The role of adipose tissue and nutrition in the regulation of adiponectin. Nutrients. 2024;16(15):2436.
17. Alzubi A, Glowacki HX, Burns JL, et al. Dose-dependent effects of short-chain fatty acids on 3T3-L1 adipocyte adipokine secretion and metabolic function. Nutrients. 2025;17(3):571.
18. Kadowaki T, Yamauchi T, Kubota N, et al. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest. 2006;116(7):1784-1792.
19. Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell. 2014;156(1-2):20-44.
20. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. J Clin Invest. 2011;121(6):2094-2101.
21. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9774):1341-1352.
22. Sümer A, Keha EE, Mentese A, Alver A. Effects of topiramate on adipocyte differentiation and gene expression of certain carbonic anhydrase isoenzymes. Turk J Biochem. 2020;45(2):217-223.
23. Pollard AE. New concepts in the roles of AMPK in adipocyte stem cell biology. Essays Biochem. 2024;68(3):349-361.
24. Scheidl TB, Wager JL, Thompson JA. Adipose tissue stromal cells: rheostats for adipose tissue function and metabolic disease risk. Can J Cardiol. 2025; Epub ahead of print.
25. Gao D, Bing C, Griffiths HR. Disrupted adipokine secretion and inflammatory responses in human adipocyte hypertrophy. Adipocyte. 2025;14(1):2485927.
26. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol. 2011;11(2):85-97.
27. Choi HM, Doss HM, Kim KS. Multifaceted physiological roles of adiponectin in inflammation and diseases. Int J Mol Sci. 2020;21(4):1219.
28. Shan Y, Chen Y, Gu H, Wang Y, Sun Y. Regulatory basis of adipokines leptin and adiponectin in epilepsy: from signaling pathways to glucose metabolism. Neurochem Res. 2023;48(7):2017-2028.
29. Chen QW, Meng RT, Ko CY. Modulating oxidative stress and neurogenic inflammation: the role of topiramate in migraine treatment. Front Aging Neurosci. 2024;16:1455858.

To Cite: Sumer A. The Effect of Topiramate on Adiponectin Secretion in 3T3-L1 Adipocytes: An *In Vitro* Approach to Anti-Obesity Mechanisms. Farabi Med J. 2025;4(3):80-87.