Comparative Meta-analysis of Adipose Tissue Transcriptomics Data in PCOS Patients and Healthy Control Women

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Abstract
Polycystic ovary syndrome (PCOS) is a common condition in reproductive-aged women that induces reproductive and metabolic derangements. Women with PCOS seem to have disturbances in lipid metabolism in the adipose tissue. Nevertheless, gene expression in adipose tissue of PCOS women and its relation to other disturbances have been fragmentarily investigated. We utilized microarray data to identify the most important up- and down-regulated candidate genes in adipose tissue of PCOS women in contrast to healthy women using the meta-analysis technique. Microarray data produced from three independent experiments ($n = 3$) conducted on adipose tissue in women with PCOS were retrieved from ArrayExpress. Then, the datasets were merged using the metaSeq package in Rstudio and differentially expressed genes (DEGs) were selected in the studies. The integrative bioinformatics analyses of candidate genes were performed by gene ontology (GO) analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis, and protein–protein interaction (PPI) network construction. Of these, 12 up-regulated genes and 12 down-regulated genes were identified and assessed as the most highly up-regulated and down-regulated genes in adipose tissue of women with PCOS. These DEGs that were annotated by KEGG analysis were mainly involved in PI3K-Akt, MAPK, Rap1, and Ras signaling pathways, and pathways in cancer such as hepatocellular carcinoma and gastric cancer, as well as metabolic pathways, and brain disorder pathways such as Alzheimer’s disease and Huntington disease pathways. In the PPI networks, PRDM10, FGFR2, IGF1R, and FLT1 were the key nodes in the up-regulated networks, while the NDUFAB1 and NME2 proteins were key in the down-regulated networks. Overall, these findings provide insight into the gene expression in adipose tissue of PCOS women and its relation to other disturbances.

Keywords Adipose tissue · DEGs · KEGG analysis · Meta-analysis · PCOS

Introduction
Polycystic ovary syndrome (PCOS) is the most common hyperandrogenic disorder affecting 5–8% of women of reproductive age [1]. PCOS is considered the foremost ovarian disease and is usually diagnosed during the early reproductive years. Most women with PCOS display some metabolic abnormalities including dyslipidemia, obesity, hyperinsulinemia, neuroendocrine abnormalities, insulin resistance, and ovulatory dysfunction [2, 3]. Moreover, PCOS is considered a multifactorial disorder with various metabolic, genetic, endocrine, and environmental abnormalities [4].

Obesity is a characteristic of 60–80% of PCOS patients and plays a critical role in the development of PCOS in many women. Obesity alters the levels of several hormones such as insulin, androgens, and adipocytokines [5]. This suggests that obesity modifies PCOS characteristics. It has been
shown that obesity has a malignant additive effect on features of PCOS such as hyperandrogenism, insulin resistance, menstrual irregularity, ovulatory disorders, and pregnancy complications [5, 6]. Hyperandrogenism or increase in secretion of androgens can induce low-grade chronic inflammation by increasing the transcription of androgen receptors in mononuclear cells [7]. Low-grade chronic inflammation itself leads to the release of adipocytokines by dysfunctional adipocytes [8].

Visceral adipose tissue is thought to be important for the pathogenesis of PCOS, because of its association with hyperandrogenemia and its often excessive accumulation in women with PCOS [9]. Increase in subcutaneous adipocytes and decrease in the secretion of adiponectin are major factors that are strongly associated with insulin resistance [10]. Furthermore, change in expression of some genes such as TWIST1, CCL2, LEPR, and PPARG in adipose tissue may be important in the pathophysiology of PCOS [11–16]. Therefore, these findings indicate that adipose tissue dysfunction may negatively affect the metabolic health of women with PCOS and thereby increase their risk for diabetes mellitus type 2 (DM2), hyperandrogenism, and cardiovascular disease [17].

A recent meta-analysis from five comparative studies has demonstrated that women with PCOS were three times more likely to develop endometrial cancer than healthy women [18]. Moreover, gene expression profiles in subcutaneous fat from no obese women with and without PCOS disclosed differences in the expression of genes encoding components of several biological pathways related to insulin and Wnt signaling, lipid metabolism, immune function, inflammation, and oxidative stress [12, 16]. By the fact that dysfunctional adipose tissue is increasingly considered to be important in the metabolic disorders in PCOS patients, in the present study, we utilized microarray data to identify the adipose tissue transcriptome changes in women with PCOS in contrast to healthy women using the meta-analysis. Additionally, this study set out to identify the role of differentially expressed genes (DEGs) in the adipose tissue of PCOS patients in different diseases, disorders, and signaling pathways.

Material and Methods

Microarray Data

To investigate the adipose tissue transcriptome changes and identify the most up- and down-regulated candidate genes in adipose tissue in women with PCOS in contrast to healthy women (control), microarray data produced from three independent experiments ($n = 3$) conducted on adipose tissue in women with PCOS were retrieved from ArrayExpress (https://www.ebi.ac.uk/arrayexpress/). In all used experiments, fat biopsy samples were obtained from morbidly obese women with or without PCOS. In the first experiment (E-GEOD-43322) which was a case–control study, we just exploited the data of 23 samples (sixteen PCOS patients and seven control). In the second experiment (E-GEOD-43264), we exploited the data of 15 samples (eight PCOS patients and seven control). In the third experiment (E-GEOD-5090), we exploited the data of 17 samples (nine PCOS patients who submitted to bariatric surgery because of morbid obesity and eight control) (Supplementary Table S1). The overall scheme of data analysis and computational tools used in this study is represented in Fig. 1. Moreover, basic characteristics of participants such as age and BMI between cases and controls in three studies are represented in Table 1.

Meta-analysis

Meta-analysis is an attempt to integrate multiple data in different studies. Indeed, by meta-analysis, all genes which

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Fig. 1 Schematic representation of data analysis and computational tools used in this study.
differentially expressed in many studies are selected as DEGs by metaSeq package [19]. Microarray studies were processed separately as individual datasets with FlexArray software version 1.6.3. The raw data were normalized using Robust Multiarray Average (RMA) algorithm and then RMA signal values were transformed into log2. Then, the datasets were merged using the metaSeq package in Rstudio, and DEGs in studies were selected. To select DEGs, P-value was adjusted in false discovery rate (FDR) as less than < 0.05, and the list of genes was obtained for adipose tissue in women with PCOS in contrast to control. Venn diagrams of all genes in three studies were generated by http://bioinformatics.psb.ugent.be/webtools/Venn/.

**Gene Ontology (GO) Analysis**

To further elucidate the functional characteristics of the most highly DEGs and to study their distribution, we used GO enrichment analysis. For this target, the most highly DEGs (12 up-regulated genes and 12 down-regulated genes) in adipose tissue from women with PCOS in contrast to control were selected and conducted using Gene Ontology Consortium tools (http://www.geneontology.org/) with default significance levels (P < 0.05). Then, the results were described in the forms of the biological process (BP), molecular function (MF), and cellular component (CC) [20].

**KEGG Pathway Enrichment Analysis**

Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis [21] was performed to identify the important pathways of the most highly up-/down-regulated genes in the adipose tissue of women with PCOS. For this target, KEGG database (http://kobas.cbi.pku.edu.cn/) was used to test the enrichment of DEGs in KEGG pathways.

**Protein–Protein Interaction (PPI) Network Analysis**

Interaction protein networks for the mentioned up and down-regulated genes in the adipose tissue of women with PCOS were constructed using the STRING v.10 (Search Tool for the Retrieval of Interacting Genes/Proteins) to detect functional association between those genes [22, 23]; this database is based on specific relationships between proteins and constructs associations based on distinct lines of evidence. It scores each protein interaction. A higher score means higher confidence in protein interaction. The most highly up/down-regulated genes in adipose tissue of women with PCOS were imported into STRING for protein interaction analysis, and the PPI network was obtained with the species limited to “Homo sapiens” and a confidence score > 0.5. All the hub genes are visible in the PPI network. In addition, according to the maximal clique centrality (MCC) scores, the highest-scored genes were selected as the hub genes. The hub genes selected from the PPI network using the MCC algorithm of the CytoHubba plugin are shown in Figs. 6 and 7.

**Results**

This study was conducted to investigate adipose tissue transcriptome changes and identify the most up- and down-regulated candidate genes in adipose tissue in women with PCOS in contrast to healthy women.

This experiment was implemented based on microarray data retrieved from three independent studies. The results illustrated that study one has 3233 DEGs, whereas DEGs in studies two and three were 1304 and 571 genes, respectively (Fig. 2). As a result, some genes were common in adipose tissue from women in three studies (Fig. 2). Number of common genes that were significantly up- and down-regulated in adipose tissue of women with PCOS in contrast to healthy women is demonstrated in Fig. 2. Additionally, the most highly DEGs (top 12 up- and down-regulated genes) in adipose tissue of women with PCOS are represented in Table 2.

**Visualization of DEG Position**

The genomic position of identified DEGs on all chromosomes of human is represented in Fig. 3. Genomic position visualization was utilized for displaying the position of identified DEGs in three studies on all human chromosomes. This work allowed us to identify which chromosome might contain more genes involved in PCOS. The chromosomal position of a gene also will help to the identification of a novel treatment for some disorders and diseases. Accordingly, the highest number of DEGs in the three studies were on chromosomes 1 and 2. Nevertheless, some chromosomes especially chromosomes 17 and 19 had a higher percentage of genes despite their smaller size. Therefore, these genes should be more considered in future PCOS studies.
Functional Classification of DEGs

GO analysis was conducted to investigate other possible functions of the DEGs detected in the adipose tissue of women with PCOS in three studies. Accordingly, comparison of GO distribution of the DEGs indicated three distinct categories: BP, MF, and CC. The most highly up-regulated genes were enriched in 95 GO functions ($P < 0.05$, Fig. 4). Of the up-regulated genes, enrichment was mainly involved in the following BP: regulation of transcription, DNA-templated, regulation of RNA biosynthetic process, regulation of gene expression, cellular nitrogen compound metabolic process, cellular aromatic compound metabolic process, and regulation of biological process, following MF: RNA binding, organic cyclic compound binding, and cation binding, and following CC: nucleoplasm part, nucleoplasm, membrane-enclosed lumen, and membrane-bounded organelle. Moreover, downregulated genes were enriched in 276 GO functions ($P < 0.05$, Fig. 4). Of the most highly downregulated genes, enrichment was mainly involved in the following BP: nucleoside monophosphate metabolic process, peptide metabolic process, immune response, intracellular transport, and organic substance metabolic process, following MF: RNA polymerase II transcription factor binding, histone binding, RNA

Table 2  The most highly DEGs in adipose tissue of women with PCOS in contrast to control women

| Ensemble ID     | Gene symbol | Gene name                                    | Log2 fold change | FDR        |
|-----------------|-------------|----------------------------------------------|-----------------|------------|
| ENSG00000066468 | FGFR2       | Fibroblast growth factor receptor 2          | 4.67321         | 0.000421   |
| ENSG00000077232 | DNAJC10     | DnaJ homolog subfamily C member 10           | 4.16549         | 0.000584   |
| ENSG00000138668 | HNRNPD      | Heterogeneous nuclear ribonucleoprotein D0    | 3.76184         | 0.000761   |
| ENSG00000170325 | PRDM10      | PR domain zinc finger protein 10              | 3.62374         | 0.000915   |
| ENSG00000140443 | IGFR1       | Insulin-like growth factor 1 receptor        | 3.49823         | 0.002893   |
| ENSG00000091879 | ANGPT2      | Angiopoietin-2                               | 3.16138         | 0.007374   |
| ENSG00000102755 | FLTI        | FMS-like tyrosine kinase                     | 3.01057         | 0.013101   |
| ENSG00000109458 | GAB1        | GRB2-associated-binding protein 1             | 2.97861         | 0.024932   |
| ENSG00000069869 | NEDD4       | E3 ubiquitin-protein ligase NEDD4             | 2.83794         | 0.025716   |
| ENSG00000204490 | TNF-α       | Tumor necrosis factor-alpha                  | 2.68917         | 0.025927   |
| ENSG00000101333 | PLCB4       | 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase beta-4 | 2.66108 | 0.027457 |
| ENSG00000120868 | APAF1       | Apoptotic protease-activating factor 1        | 2.37294         | 0.027933   |
| ENSG00000088832 | FKBPA1      | Peptidyl-prolyl cis–trans isomerase FKBPA1    | −5.30816        | 0.000035   |
| ENSG00000243678 | NME2        | Nucleoside diphosphate kinase B               | −4.84912        | 0.000074   |
| ENSG00000168032 | ENTPD3      | Ectonucleoside triphosphate diphosphohydrolase 3 | −4.75045 | 0.000238 |
| ENSG00000078295 | ADCY2       | Adenylate cyclase type 2                     | −4.53719        | 0.000641   |
| ENSG00000004779 | NDUFA1      | Acyl carrier protein, mitochondrial          | −4.46018        | 0.000962   |
| ENSG00000082515 | MRPL22      | 39S ribosomal protein L22, mitochondrial     | −4.06421        | 0.002856   |
| ENSG00000180424 | DEFB1       | Beta-defensin 1                              | −3.75248        | 0.006187   |
| ENSG00000189223 | PAX8-AS1    | Paired-box gene 8                            | −3.70671        | 0.007413   |
| ENSG00000164308 | ERAP2       | Endoplasmic reticulum aminopeptidase 2       | −3.59318        | 0.007682   |
| ENSG00000145777 | TSLP        | Thymic stromal lymphopoietin                 | −3.16270        | 0.009814   |
| ENSG00000163106 | HPGDS       | Hematopoietic prostaglandin D synthase       | −2.86374        | 0.023781   |
| ENSG00000177868 | SVBP        | Small vasohibin-binding protein              | −2.79582        | 0.031863   |
polymerase II regulatory region sequence-specific DNA binding, DNA-binding transcription factor activity, and following CC: mitochondrial respiratory chain complex I, NADH dehydrogenase complex, respiratory chain complex I, ribosomal subunit (Supplementary Table S2).

KEGG Enrichment Analysis

KEGG enrichment analysis of the most highly DEGs revealed several pathways to gain greater perception into mechanisms of DEG biological functions in the adipose tissue of women with PCOS (P < 0.05, Fig. 5). KEGG enrichment analysis demonstrated that the most highly up-regulated expression genes were assigned into 4 pathways where the largest categories were involved in the metabolic pathways and pyrimidine metabolism (Fig. 5). The complete significant KEGG pathways for the most highly DEGs are provided in Supplementary Table S3.

PPI Networks

To explore the regulation mechanism of key DEGs in the adipose tissue of women with PCOS, the most highly DEGs were imputed into STRING to construct a PPI network, and the network was visualized for up- and down-regulated genes separately (Figs. 6 and 7). In PPI networks, the most highly up/down-regulated genes with the highest hub scores were identified as hub genes (Figs. 6 and 7). Hub genes play a determinant role in gene regulation because of their central position in the network. In the PPI networks of the most highly DEGs, PRDM10, FGFR2, IGF1R, and FLT1 were the key nodes in the up-regulated networks (Fig. 6), while the NDUFAB1 and NME2 proteins were key in the down-regulated networks (Fig. 7). These genes with the highest hub scores were identified as hub genes that highly correlated with these pathway-related genes, suggesting their regulatory function.

Discussion

Given the central role of adipose tissue in the development of PCOS in overweight and obese women, this comparative meta-analysis was performed to show changes in the expression patterns of genes between adipose tissue of PCOS women and control samples. Our result showed changes in the expression patterns of several genes in the adipose tissue of PCOS women and their relation to future possible disturbances. In our meta-analysis study, the majority of significantly enriched pathways were involved in immune diseases, cancer, metabolic pathways, and insulin secretion emphasizing a critical role in the pathogenesis of PCOS.

In the present study, we found that TNF-α and ANGPT2 genes were dramatically up-regulated in the adipose tissue of PCOS women in contrast to healthy women (Table 1). The role of these up-regulated genes has been demonstrated in PCOS pathogenesis and cancer. Tumor necrosis factor α (TNF-α) is a pro-inflammatory cytokine and thought to play a role in the pathogenesis of PCOS [24]. Although TNF-α is involved in adipocyte metabolism [25], it has been reported that mRNA expression of TNF-α is similar levels in adipose tissue of women with and without PCOS [17]. Meanwhile, TNF-α causes insulin
resistance in adipose tissue [25] and maybe affects the onset of type 2 diabetes mellitus (T2DM) [26]. T2DM and insulin resistance stimulate ovarian and adrenal androgen production and lead to PCOS [27]. Although the ovaries are the main source of increased androgen (hyperandrogenism) in PCOS [28], adrenal androgen excess can be present in approximately 20–25% of women with PCOS [29]. Thus, hyperandrogenism has a multifactorial origin and overexpression of TNF-α is also one of them. Of note, overexpression of TNF-α can trigger the delivery of Angiopoietin-2 (ANGPT2) into the blood [30]. ANGPT2 is a growth factor regulating vessel growth and maturation during angiogenesis [31]. ANGPT2 is expressed by
Fig. 5 KEGG enrichment analyses of the most highly DEGs in adipose tissue in women with PCOS in contrast to control women. The size of $P$-value is associated with each color in color scale bar and the size of dot reflects the number of DEGs in each pathway. Rich factor (%) is the ratio of the number of differentially expressed genes annotated in a pathway to the number of all genes annotated in this pathway.

Fig. 6 Gene network of the most highly up-regulated genes in adipose tissue in women with PCOS in contrast to control women. The connection difference colors represent the types of evidence for inferring association: recurring neighborhood in different genomes (green line), co-occurrence of those genes in the same organisms (dark blue), experimental protein–protein interaction data (pink), events of gene fusion (red), co-expression (black), pathway described by other databases (light blue), literature text-mining (yellow), and homology (purple lines).
activated endothelial cells under usual conditions. ANGPT2 also can be produced by mesenchymal stem cells and by tumor cells in hypoxia and cancer conditions. In addition to its proangiogenic role during cancer progression, ANGPT2 contributes to metastatic formation [32]. It has been reported that ANGPT2 is a prognostic factor in localized metastatic colorectal cancer (CRC) [33]. Therefore, up-regulation of ANGPT2 in adipose tissue of PCOS women might be considered as a biomarker in the early detection of cancer.

Our meta-analysis result showed that the expressions of HPGDS and TSLP genes were dramatically down-regulated in the adipose tissue of women with PCOS (Table 1). HPGDS is a sigma-class glutathione transferase expressed in peripheral tissues such as the placenta, intestine, and adipose tissue [34] and catalyzes the isomerization of prostaglandin H2 (PGH2) to prostaglandin D2 (PGD2) [35]. Inhibiting the production of PGD2 by inhibiting HPGDS may make it an interesting target to treat allergic inflammation [36]. HPGDS may play a role in the regulation of inflammation and epithelial cell health within the oviduct, an effect likely required to maintain homeostasis and function of this key reproductive organ [37]. In our study, HPGDS expression was down-regulated in the adipose tissue of women with PCOS; however, investigation of HPGDS-regulated inflammation in PCOS disorder should be examined.

Another interesting gene among the most highly down-regulated in adipose tissue of women with PCOS was thymic stromal lymphopoeitin (TSLP), which acts as a co-stimulator for thymocyte proliferation [38]. Recent studies have reported

![Gene network of the most highly down-regulated genes in adipose tissue in women with PCOS in contrast to control women. The connection difference colors represent the types of evidence for inferring association: recurring neighborhood in different genomes (green line), co-occurrence of those genes in the same organisms (dark blue), experimental protein–protein interaction data (pink), events of gene fusion (red), co-expression (black), pathway described by other databases (light blue), literature text-mining (yellow), and homology (purple lines).](image-url)
an expanding role of TSLP in inflammatory diseases and cancer [38]. Moreover, it has been found that overexpression of TSLP (in K14-TSLP transgenic mice) can inhibit the development of early breast cancer [39]. Expression of TSLP has been reported in visceral human adipose tissue [40, 41]. However, the level of mRNA expression of TSLP is lower in obese women with metabolic syndrome (state of insulin resistance associated with central obesity) compared to those without metabolic syndrome [40]. The association of abdominal central obesity with insulin resistance and T2DM characterizes many patients with PCOS [42]. Therefore, activation of TSLP signaling may be a therapeutic immunotarget for improving insulin sensitivity and preventing T2DM [43].

Of the most highly DEGs, two up-regulated genes (FGFR2 and IGF1R) in the adipose tissue of women with PCOS were the key nodes in the up-regulated PPI networks (Fig. 6). Fibroblast growth factor receptor 2 (FGFR2) has a critical role in mammary development [44] and in the maintenance of breast tumor-initiating cells [45], thus has been identified as a breast cancer risk [46]. Low expression of FGFR2 is associated with lower numbers of breast tumor-initiating cells [45]. Insulin-like growth factor receptor (IGF1R) regulates androgen biosynthesis and is involved in insulin secretion and action [47]. Dysregulation of the IGF-1/insulin/IGF-1R system may contribute to the pathophysiology of PCOS [48]. Therefore, overexpression of FGFR2 and IGF1R genes in the adipose tissue of women with PCOS may be associated with the risk for breast cancer.

In this meta-analysis study, GO enrichment analysis of DEG targets revealed several pathways to gain a more excellent perception of DEGs’ biological process. The results for GO enrichment analysis in terms of biological process showed that DEGs in adipose tissue from PCOS patients are related to several significantly enriched terms including glutathione derivative biosynthetic process, oxidative phosphorylation, peptide metabolic process, and immune response. The glutathione derivative biosynthetic process is chemical reactions and pathways resulting in the formation of glutathione derivative. Glutathione biosynthesis is essential for cellular redox homeostasis and antioxidant defense [49]. Dysregulation of glutathione biosynthesis has been described in several pathological conditions including liver injury [50], diabetes [51], neurological disorders [52], organ fibrosis [53], and cardiovascular disease [54]. Similarly, dysregulation of glutathione biosynthesis in hepatocytes leads to steatosis that may be accompanied by mitochondrial damage and hepatic failure [55]. Moreover, glutathione biosynthesis is critical for immune cell function and several reports have illustrated this fact, in particular in the context of the immune response and T-cell activation [56]. Interestingly, in our Go enrichment analysis, DEGs also were directly related to oxidative phosphorylation and immune response.

On the other hand, KEGG pathway analysis of DEG targets revealed several pathways to gain a more excellent perception of the mechanisms of DEG pathways. KEGG analysis results showed that DEGs in adipose tissue from PCOS patients are related to several signaling pathways including PI3K-Akt, MAPK, Rap1, and Ras signaling pathways, and pathways in cancer such as hepatocellular carcinoma and gastric cancer. Among these, MAPK signaling pathway, PI3K-Akt signaling pathway, Rap1 signaling pathway, and Ras signaling pathways have been reported to be involved in the control of cell proliferation, apoptosis, and cancer [57–59]. The Ras signaling pathway activates several other effector pathways, especially the PI3K-Akt signaling pathway [59].

In confirmation of our results, whole-genome RNA sequencing analysis on single oocyte of women from Mongolia with PCOS has shown alteration in several DEGs in pathways in cancer, MAPK signaling pathway, and PI3K-Akt signaling pathway in contrast to females with normal ovulation [60]. It has been increasingly recognized that PI3K plays an important role in PCOS. Previous studies have shown that activation of the PI3K-protein kinase B (Akt) signaling pathway has important effects on insulin resistance and endometrial cancer [61]. The PI3K-Akt signaling pathway disorders can not only affect follicular development but also cause diseases, such as tumors [62, 63]. Chen et al. [64] investigated the mice treated with cyclophosphamide (CTX) and found that CTX could lead to follicular loss via the PI3K-Akt-mTOR signaling pathway in ovaries. It indicated to some extent that the PI3K-Akt signaling pathway was related to follicular apoptosis. Hyperandrogenism is another characteristic of PCOS, and it is related to the PI3K-Akt signaling pathway [61].

**Conclusion**

In conclusion, as adipose tissue is important for the pathogenesis of PCOS, this study provides more insight into the gene expression in adipose tissue of PCOS women and its relation to other disturbances. We showed that PCOS is associated with aberrant adipose tissue genes expression with dysregulated pathways including PI3K-Akt, MAPK, Rap1, and Ras signaling pathways, and pathways in cancer such as hepatocellular carcinoma and gastric cancer, as well as metabolic pathways. This is a meta-analysis study and the cause-and-effect relationship was not clear; therefore, it is not possible to infer that PCOS alters the adipose tissue gene expression or contrariwise. Nevertheless, our findings need to be confirmed in prospective studies. Therefore, further studies are recommended.

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Data Availability Not applicable.

Code Availability All software applications or custom codes were presented in the “Material and Methods” section.

Declarations

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

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