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Research

Poly-*p*-dioxanone Thread Leads to Fat Metabolism Around the Thread in Pig Subcutaneous Back Fat

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Abstract

Background: When poly-*p*-dioxanone (PDO) thread is implanted subcutaneously, in addition to collagen hyperplasia, it can also cause denaturation of surrounding adipocytes and reduce the thickness of the fat layer. Hitherto, no studies have thoroughly investigated the effects of PDO thread on adipose tissue.

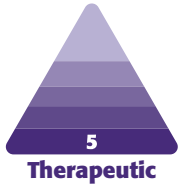
Objectives: In this study, the effect of PDO thread on adipose tissue was investigated in an animal model.

Methods: In the current study, PDO thread was implanted into subcutaneous adipose tissue of the back in a miniature pig. Implantation site tissue and control site tissue were taken 12 weeks after implantation for hematoxylin and eosin (H&E) staining and transcriptome sequencing. Gene ontology functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes pathway analysis were performed to investigate the differential gene expression between PDO thread implantation and control site tissue.

Results: An obvious decrease in the number, fusion, and denaturation of adipocytes can be seen by H&E staining. Sequencing analysis results showed that many of the genes identified, which were downregulated after PDO thread implantation, were involved in functions and pathways related to lipid metabolism, such as fatty acid metabolism, fatty acid degradation, and lipid cell lipolysis regulation. Some genes related to fatty acid metabolism were significantly downregulated in the PDO tissue at 12 weeks compared to the control tissue.

Conclusions: Our results showed PDO thread implantation can cause a decrease in the number of adipocytes, as well as a significant alteration of the expression levels of some genes involved in lipid metabolism-related pathways. PDO thread might play an important role in promoting lipolysis.

Level of Evidence: 5



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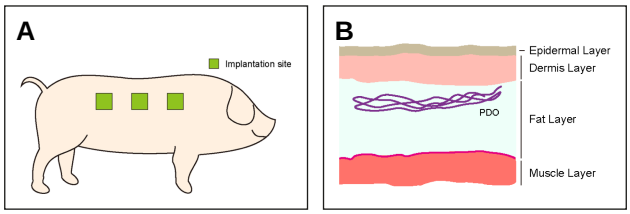

Figure 1. Illustration of the implantation site. (A) The implantation site located on the dorsal region of the pig. (B) The implantation site of poly-*p*-dioxanone (PDO) thread within the subcutaneous adipose tissue layer.

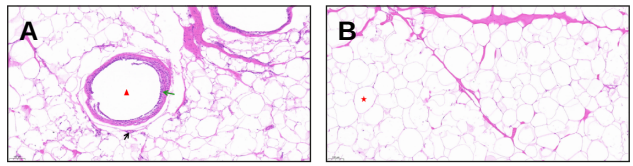

Figure 2. Hematoxylin and eosin staining. (A) The poly-*p*-dioxanone (PDO) thread implantation site tissue: implantation site (the triangle), capsule-like structure (the thin arrow), and new genetic small vessel (the thick arrow). (B) The control site tissue: normal subcutaneous adipocyte (the star). Scale bar: 100 μm.

As adults grow older, their metabolic rate decreases, and fat can accumulate in different parts of the body, resulting in things such as a double chin, bat wings, and increased belly fat.[1] In recent decades, with improvements in global economic levels and people's living standards, more people have begun to pay increased attention to their appearance and seek medical methods to improve the fat they have accumulated with age. Patients' fear of surgery has made minimally invasive and noninvasive fat reduction technology a research focus in recent years.[2] According to the data released by the International Society of Aesthetic Plastic Surgery in 2020, liposuction surgery has exhibited a downward trend compared with previous years, and the number of nonsurgical fat reduction procedures performed has increased significantly compared with previous years.[3]

As a new nonsurgical method, thread implantation is gradually flourishing in the medical cosmetology industry due to the unique properties of its products. The material used in thread technology has developed from the original nonabsorbable thread (mostly polypropylene) to the current absorbable thread. One of the common absorbable thread materials currently on the market is poly-*p*-dioxanone (PDO) thread.[4] It has been clinically confirmed that absorbable PDO thread has excellent mechanical properties, enabling it to lift sagging subcutaneous tissue and restore it to its original position, and it also exhibits good biocompatibility, and a capacity to exert local stimulation that induces new collagen, achieving the intended rejuvenation. In 1 study in which PDO thread was implanted into the subcutaneous adipose tissue of a pig, in addition to collagen hyperplasia around the thread, denaturation of the surrounding adipocytes and reduction of the thickness of the fat layer were observed, and they remained 1 year after implantation.[5]

To date, no studies have further investigated the effects of PDO thread on fat. In the current study, the pig was selected as an experimental animal because of its abundant subcutaneous fat, which is similar to that of human skin. Bioinformatics technology was used to explore changes in gene expression levels in local adipose tissue after PDO thread implantation, to investigate the specific mechanism of local lipid metabolism after PDO thread implantation, and expand new ideas for the clinical application of PDO.

METHODS

Experimental Animal and Materials

Among the commonly used experimental animals, the skin structure of pigs is more similar to that of humans, so a Guangxi Bama miniature pig (28.5 kg, 12 months old) was selected as the test animal in this study. The implantation material was sterilized and packaged PDO embedding thread (diameter 2-0, length 75 cm). An 18G needle was used for percutaneous puncture during embedding. The thread and needle were provided by Imeik Technology Development Co., Ltd. (Beijing, China). The experimental protocol was approved by Institutional Animal Care and Use Committee (IACUC) of Beijing Kuibushichuang Biotechnology Co., Ltd. (Beijing, China). The animal IACUC number is SC2021-07-011. All methods were performed in accordance with the relevant guidelines and regulations, including the ARRIVE guidelines. This study was conducted from December 2021 to June 2022.

Experimental Operation

The pig was allowed to acclimate for 7 days prior to the initiation of the formal experiment. Before PDO thread implantation, the pig was weighed and anesthetized through intramuscular injection. The back hair was then removed, and the pig was transferred to the test bench. Tracheal intubation was performed, and an intravenous channel was established while vital signs were monitored. The back area was disinfected with iodophor and 75% alcohol spray, and at least 3 implantation areas (3 × 3 cm each) were selected for marking, with at least 3 cm spacing between each implantation area (Figure 1). The thread was placed in an 18G needle, the needle handle was held, a needle

insertion point in the implantation area was selected, and the whole thread was implanted into the subcutaneous fat layer on the back of the pig in a fan-shaped arrangement. Twelve weeks after implantation, the pig was killed, and implantation site tissue ($n = 3$) and control site tissue ($n = 3$) were collected. The blank tissue at the unimplanted site of the pig back was selected as the control site tissue. The prepared tissue was fixated using a 10% formalin solution, embedded with paraffin, sliced into pieces and then stained using hematoxylin and eosin (H&E) staining. Besides, a piece of tissue with the size of a soybean grain was selected and cryopreserved in liquid nitrogen. The frozen samples were sent for genetic testing.

Pathological Analysis

H&E staining was performed to mainly observe the morphological changes of subcutaneous adipocytes around the thread body.

Bioinformatics Analysis

The *t* test was used to assess differential gene expression levels in experimental and control tissues, and the differentially expressed genes identified were assessed through gene ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. GO functional enrichment analysis and KEGG pathway analysis were conducted using the DAVID website (https://david.ncifcrf.gov/), and the R programming language 3.6.2 was used for analysis and photographing. $P < .05$ was deemed to indicate statistical significance.

RESULTS

Clinical Observation

Although the degradation time of PDO thread is 6 months, when it is implanted in vivo, the thread shape can usually be maintained until 12 weeks, so 12 weeks were selected as the observation time point in the current study.[4] The pig successfully endured the adaptation period, husbandry proceeded unproblematically after the operation, and the pig exhibited no abnormal conditions. No abnormal phenomena such as erythema, hemorrhaging, or crusting of the skin at any implantation site were evident during autopsy. There were no differences between the tissues at each implantation site and the control tissues, as determined through visual observation. Gene sequencing was conducted successfully, and the quality of the samples was qualified.

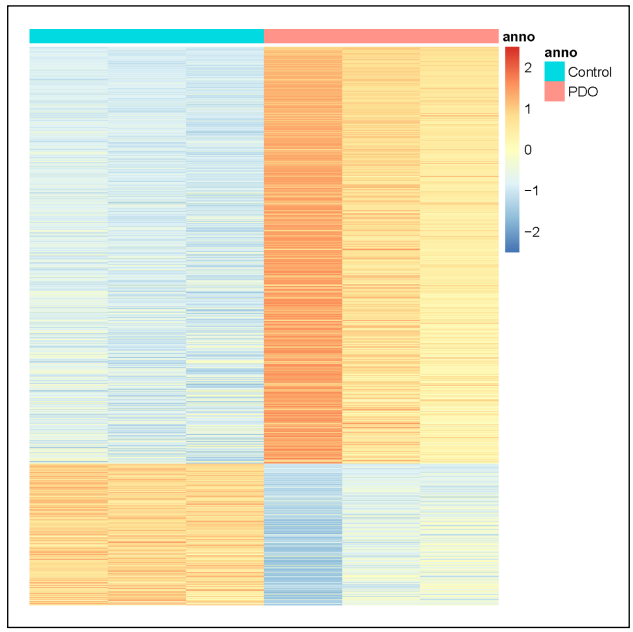

Figure 3. Differentially expressed gene heat map. Different columns in the graph represent different samples, and different rows represent different genes. The color represents the expression level of the gene in the sample.

Pathological Observation

When observed by H&E staining, the fibrocystic structure can be clearly seen surrounding the thread body, and fibroblasts and inflammatory cells were aggregated in the capsule-like structure. Neogenetic small vessels can also be visible around the thread. Meanwhile, the adipocytes surrounding the thread show an obvious decrease in number, fusion, and denaturation, which is obviously different from normal subcutaneous adipocytes (Figure 2).

Differential Gene Expression Analysis

A total of 3835 significantly differentially expressed genes were identified. Among them, 2864 were upregulated in the PDO group and 971 were downregulated. Heat maps were generated to represent the distributions of differentially expressed genes in different tissues (Figure 3).

GO functional enrichment analysis indicated that many of the genes downregulated after PDO implantation were related to fatty acid metabolism and lipid transport, such as fatty acid β-oxidation, lipid metabolic processes, the tricarboxylic acid cycle, white fat cell differentiation, and positive regulation of lipoprotein lipase activity. The upregulated differentially expressed genes were mainly involved in functions related to apoptosis, such as positive regulation of apoptotic processes, cellular responses to low-density

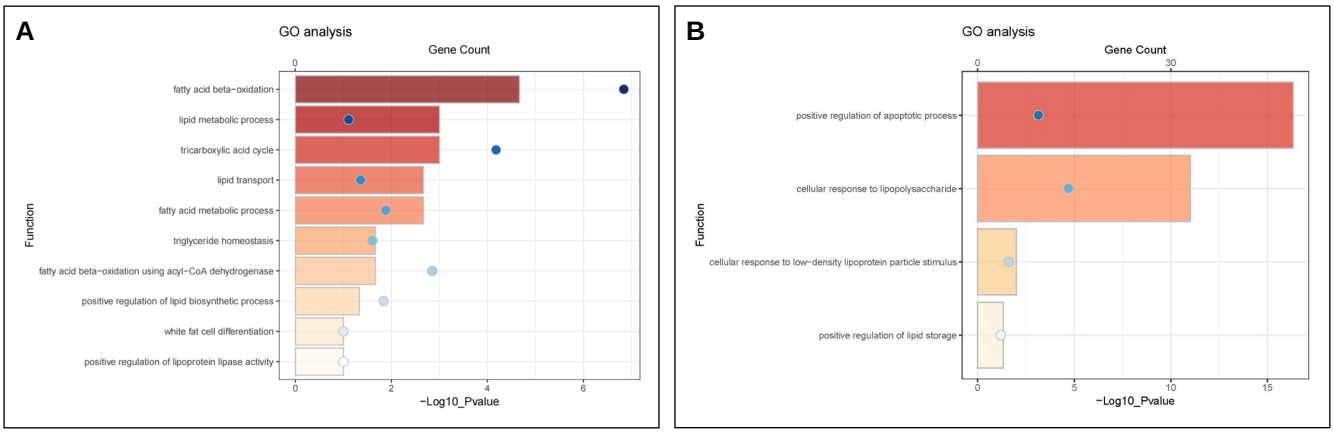

Figure 4. Gene ontology (GO) analysis. (A) GO analysis of downregulated genes. (B) GO analysis of upregulated genes.

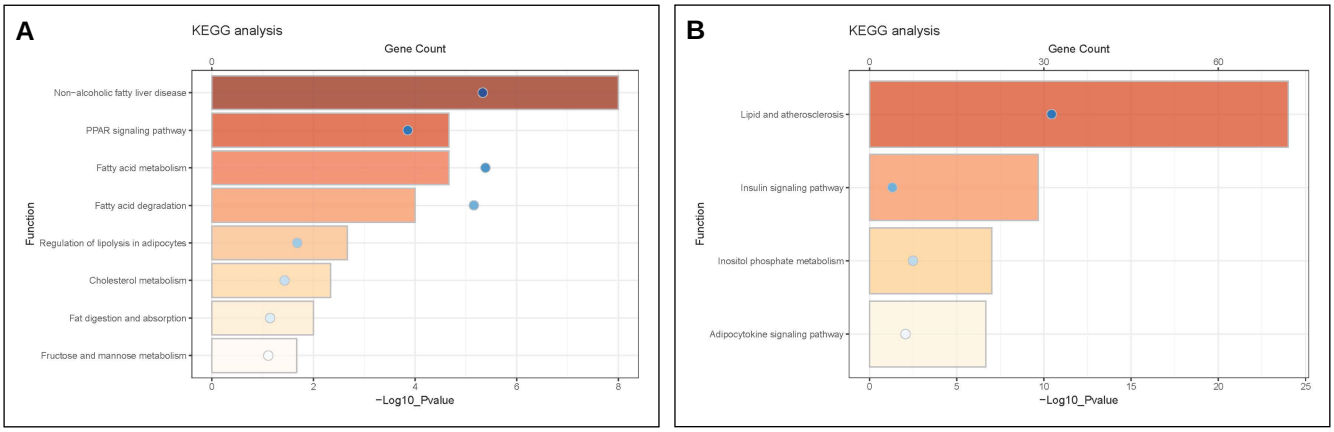

Figure 5. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. (A) KEGG analysis of downregulated genes; (B) KEGG analysis of upregulated genes.

lipoprotein particle stimulus, and positive regulation of lipid storage (Figure 4).

In KEGG analysis of the differentially expressed genes downregulated after PDO implantation, many were associated with pathways related to lipid metabolism, such as the peroxisome proliferator–activated receptor (PPAR) signaling pathway, fatty acid metabolism, fatty acid degradation, lipolysis regulation in adipocytes, and fat digestion and absorption. The upregulated differentially expressed genes were mainly associated with pathways related to lipid metabolism, or involved in the regulation of fatty acid metabolism, such as atherosclerosis, the insulin signaling pathway, and the adipocytokine signaling pathway (Figure 5).

Further analyses of the differentially expressed genes were performed with reference to the above-described key pathways, including fatty acid metabolism and the PPAR signaling pathway. Expression of genes involved in key pathways in the PDO tissues such as acetyl-CoA carboxylase alpha (*ACACA*), acetyl-coenzyme A acyltransferase 2 (*ACAA2*), stearoyl-CoA desaturase (*SCD*), cytosolic malic enzyme 1 (*ME1*), enoyl-CoA hydratase and 3-hydroxyacyl CoA dehydrogenase (*EHHADH*), fatty acid binding protein 7, peroxisome proliferator activated receptor alpha (*PPARA*), and peroxisome proliferator activated receptor gamma (*PPARG*) was significantly downregulated ($P < .05$). Acyl-CoA synthetase long chain family member 4, phospholipid transfer protein, and oxidized low-density lipoprotein receptor 1 were significantly increased. Genetic analysis pertaining to key pathways is shown in Figure 6.

DISCUSSION

In this study, genes expressed in the subcutaneous adipose tissue of a pig implanted with PDO thread were sequenced using transcriptome sequencing technology. Compared

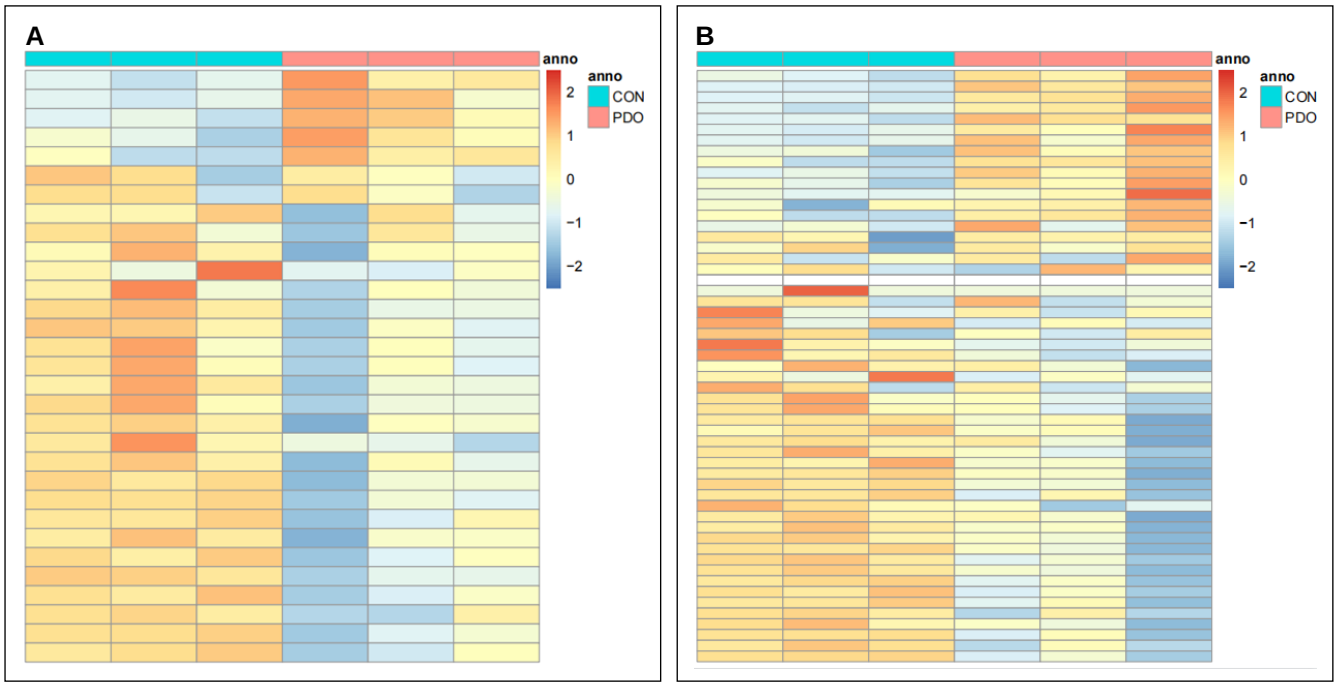

Figure 6. Differentially expressed gene heat maps. Different columns represent different samples, and different rows represent different genes. The color represents the expression level of the gene in the sample. (A) Fatty acid metabolism. (B) Peroxisome proliferator–activated receptor signaling pathway. CON, control tissue; PDO, poly-*p*-dioxanone implantation tissue.

with unimplanted control tissue, a total of 3835 significantly differentially expressed genes were identified, of which 2864 were upregulated and 971 were downregulated. GO functional analysis and KEGG pathway enrichment analysis indicated that many of the genes downregulated after PDO implantation were involved in functions related to lipid metabolism such as fatty acid β-oxidation, and pathways related to lipid metabolism such as fatty acid metabolism, fatty acid degradation, and lipid cell lipolysis regulation. Further research on specific genes revealed that *ACACA*, *SCD*, *EHHADH*, and other genes related to fatty acid metabolism were significantly downregulated compared to control tissue, indicating that the implantation of PDO thread may play an important role in the promotion of lipolysis through these genes. Meanwhile, tissue samples from the thread implantation site and control site were collected and analyzed by H&E staining. An obvious morphological difference between the 2 groups can be observed. A decrease in the number, fusion, and denaturation of the adipocytes can be seen clearly surrounding the thread, which also indicated that implantation of the thread might cause localized lipid metabolism.

Numerous studies have demonstrated that when PDO thread is implanted into the skin, it can cause local irritation in the skin tissue, thereby inducing the tissue to produce new collagen, and improving the state of skin aging and sagging.[6-8] Yoon et al reported that after implanting PDO thread into the subcutaneous adipose tissue of pigs, in addition to collagen hyperplasia around the thread, denaturation of the surrounding adipocytes and reduction of the thickness of the fat layer were observed, which is consistent with our study.[5] Moreover, the collagen generated around the thread was connected to the inherent fibrous connective tissue of the body to form a “fibrous bridge” which changed the structure of the original adipose tissue, and this phenomenon could last for 1 year. Hitherto, however, no study has investigated changes in adipose tissue-related gene pathways caused by the implantation of PDO thread.

With the continuous development of minimally invasive and noninvasive diagnosis and treatment technology in recent years, a variety of rapid nonsurgical lipolysis procedures without hospitalization have emerged, including injection (chemical) lipolysis, ultrasonic lipolysis, cryolipolysis, radiofrequency lipolysis, and laser lipolysis.[2,9,10] These lipolysis techniques destroy the structural integrity of fat cells through medicinal chemistry, low temperatures, acoustic cavitation of ultrasonic waves, photoablation through lasers, and light modulation, such that triglycerides in cells are metabolized after efflux and promote lipid metabolism, triggering the body's own repair mechanisms, thus achieving the aim of localized fat dissolution.[9-13] However, the various above-described techniques are prone to causing complications of varying degrees, such as localized tissue necrosis, allergy, panniculitis, and localized scarring.[14] As a new type of absorbable material, PDO

has good biocompatibility and is widely used in various fields. When it is used for body shaping and facial rejuvenation in the field of aesthetic medicine, generally the only potential complications are bruising, bleeding, redness, and other complications that can be recovered from in a short time.[4,15] Embedding PDO threads around fibrous connective tissue can increase tissue thickness and connect existing fibrous connective tissue, thus stimulating and reinforcing soft tissue. Our study has demonstrated the regulatory effects of PDO threads on adipose tissue, but this effect is only limited to the adipocytes around the suture threads and does not extend to the entire layer, so the ability of PDO threads to regulate adipose tissue is within a controllable range. It can also be used in combination with other beauty programs, and to date, its reported safety has been relatively good.[16,17] However, our study suggests that the clinical use of a substantial number of threads may potentially induce degeneration in the adipose tissue, resulting in noticeable contour changes, which also raises a cautioning effect for clinical combination use.

In the current study, the implantation of PDO thread was associated with changes in the expression of multiple genes related to lipid metabolism. *ACACA* is an important regulatory gene in the fat metabolism pathway, a key rate-limiting enzyme in the de novo synthesis of fatty acids, and plays an important role in the biosynthesis of fatty acids.[18] *ACAA2* is a key enzyme in fatty acid oxidation. It can catalyze the β-oxidation of fatty acids and participate in fatty acid metabolism. It is a key gene in the lipid metabolism pathway. In a study that utilized sheep preadipocytes, *ACAA2* knockout inhibited the formation of lipid droplets and inhibited the differentiation of adipocytes.[19] *SCD* is a rate-limiting enzyme that catalyzes the formation of monounsaturated fatty acids from saturated fatty acids, and is an important target for the control of fatty acid metabolism.[20] At the individual level, mice with full gene knockout of *SCD1* (a subtype of *SCD*) exhibited accelerated energy metabolism manifested by enhanced lipid oxidation, reduced synthesis, and enhanced insulin sensitivity, and could resist high-carbohydrate and high-fat diet-induced obesity and fatty acid denaturation.[21] *ME1*, *PPARA*, *PPARG*, and other genes are also evidently involved in lipid metabolism regulation and adipocyte differentiation.[22,23] The expression levels of these genes were significantly reduced in the PDO group, indicating that they play an important role in promoting lipid metabolism or inhibiting adipocyte differentiation.

The present investigation was an exploratory study in which only the most widely used PDO thread was tested. Whether the implantation of other types of threads will have the same effects remains to be determined. In addition, the study only conducted gene sequencing analysis at the midpoint of the theoretical degradation of the thread. Whether the expression of related genes at other time points will have different effects requires further research.

CONCLUSIONS

PDO thread is a safe biomaterial that may cause a number decrease, fusion, and denaturation in when it is implanted subcutaneously. It can also cause localized lipid metabolism by regulating genes in related pathways. The effects of its clinical application require more in-depth research and associated clinical data.

Acknowledgements

The datasets generated (the raw sequencing data) during the current study are available in the Genome Sequence Archive (Genomics, Proteomics & Bioinformatics 2021) in National Genomics Data Center (*Nucleic Acids Res* 2022), China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of Sciences.

Disclosures

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