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Predictors of slowing down the wound healing in overweight patients

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ABSTRACT

Objective. To identify possible predictors of slowing down the wound healing in overweight individuals seeking for aesthetic plastic surgery.

Material and methods. The study included female patients who applied for contour plastic surgery of the mammary glands and anterior abdominal wall for aesthetic indications. We identified 3 groups of patients in postoperative period depending on wound healing process: group 1 — complicated wound process (skin healing for more than 21 days, ligature-related fistula, seroma) (*n*=21; 42.86%); group 2 — delayed wound healing (skin healing for 14-21 days) (*n*=16; 32.65%); group 3 — standard wound healing (skin healing up to 14 days) (*n*=12; 24.49%). We analyzed 23 factors regarding the effect on wound healing: pro-inflammatory interleukins including tumor necrosis factor α (TNF-α), IL-1β, IL-6, IL-8 (pg/ml); markers of inflammation including C-reactive protein (CRP) (mg/l), leukocytes (109/l); fat-soluble vitamins E, A, D, K (mcg/ml); indicators of carbohydrate metabolism including insulin (mME/l), glucose (mmol/l), HOMA-IR insulin resistance index; absolute number (10^9) of rod-shaped and segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils.

Results. Predictors of complicated wound healing in overweight patients undergoing plastic surgery for aesthetic indications are HOMA-IR insulin resistance index ≥3.1, serum insulin ≥14.0 mMU/l and IL-1ß (spontaneous release) ≥45.0 pg/ml.

Conclusion. Identification of these factors in preoperative period will make it possible to predict unfavorable course of wound process and determine treatment strategy.

Keywords: *overweight, wound process, inflammation, prognosis, long-term non-healing wound, breast contouring, contouring of anterior abdominal wall.*

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Introduction

In the last years, the number of aesthetic surgeries has been steadily increasing all over the world. Most of these procedures imply harvesting of different flaps and their displacement relative to each other. Therefore, understanding the pathophysiology of wound process and mechanisms of tissue repair is an important component of plastic surgery.

Wound healing is a complex and multicomponent process based on inflammation, regeneration and fibrosis [11]. Sequence of these processes is provided by interaction of various cells through cellular mediators and direct intercellular contacts. Many growth factors and cytokines released by cells are involved in regulation of wound process and epithelialization of defect [9, 12].

Polymorphonuclear leukocytes are key cells in early phase of inflammation. These cells eliminate microbial agents and non-viable tissues. Leukocyte granules can play the role of inflammatory mediators. The content of neutrophilic leukocytes is maximal within 24-48 hours after injury and decreases later. At the later stages of inflammation, monocytes/macrophages acquire a significant role and actively release pro-inflammatory cytokines and fibrogenic growth factors [10]. There are also lymphocytes in the focus of inflammation. These cells appear in the wound together with monocytes and then again together with plasma cells and provide immune control of regeneration process [9]. Mast cells having various regulatory functions throughout wound healing are also important.

In proliferative phase of wound healing, the wound defect is filled with granulation tissue. This tissue is formed mainly due to proliferating fibroblasts, tissue macrophages and neovascularization [4]. Fibroblasts release various substances to ensure normal process of wound healing including glycosaminoglycans and collagen. These substances contribute to formation of connective tissue scar and less area of the wound [6]. Fibroblasts need oxygen, amino acids, vitamins and microelements for normal functioning. In remodeling phase, wound surface is replaced by dense scar. The number of fibroblasts and macrophages and growth of capillaries gradually decrease.

Non-healing and complicated wounds are usually characterized by certain defects in the phase of inflammation and/or regeneration, while intercellular and cell-matrix interactions are disturbed [1]. Inflammatory process in non-healing wounds undergoes significant changes and becomes chronic. There are simultaneous signs of all phases of the wound process [2].

There are multiple factors contributing to unfavorable course of the wound process: accumulation of non-viable

tissues, infectious agents, impaired release of growth factors, cytokines, proteases, cellular and extracellular components, poor perfusion of wound edges, oxidative stress, reduced content of bioelements [7, 12, 13].

Wound healing is slowed down in people with impaired carbohydrate metabolism and obesity that is associated with impaired release of growth factors and cytokines [3, 8].

The purpose of the study was to identify possible predictors of slowing down the wound healing in overweight individuals seeking for aesthetic plastic surgery.

Material and methods

The study included 49 women aged 30-60 years (mean 46.9±7.1) with a body mass index >25 kg/m^2 (mean 31.6±5.0) and waist circumference > 80 cm. All patients underwent elective plastic surgeries between 2016 and 2018 (breast and anterior abdominal wall contouring). Three groups were distinguished in postoperative period depending on the course of wound process: group 1 — complicated wound process (recovery of integumentary tissues for more than 21 days, fistulas, seromas) (*n*=21; 42.8%); group 2 — delayed wound process (recovery of integumentary tissues within 14—21 days) (*n*=16; 32.6%); group 3 — standard wound process (recovery of integumentary tissues within 7—14 days) (*n*=12; 24.5%).

We analyzed the influence of 23 factors on wound healing process:

— pro-inflammatory interleukins (IL): tumor necrosis factor α (TNF-α), IL-1β, IL-6, IL-8 (pg/ml);

— inflammation markers: C-reactive protein (CRP) (mg/l), leukocytes (10^9/l);

— fat-soluble vitamins E, A, D, K (μg/ml);

— indicators of carbohydrate metabolism: insulin (mIU/l), glucose (mmol/l), insulin resistance index HOMA-IR;

— clinical blood test: absolute number (10^9) of stab and segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils.

Data are presented as median (Me) and interquartile range [Q25; Q75]. Non-parametric Kruskal–Wallis test was used for between-group comparison, Pearson χ^2 test — for comparison of binary and nominal indicators. Differences were significant at p-value<0.05. Univariate logistic regression was applied to identify risk factors of unfavorable course of wound process. Statistical analysis was carried out using the Statistica 10 and SAS JMP 11 software package.

Results and discussion

There were no significant between-group differences in pro-inflammatory interleukins and inflammation markers (p>0.05).

We found significant differences in the content of vitamin A. Vitamin A is known to stimulate growth of epithelium, fibroblasts, granulation tissue, angiogenesis, collagen synthesis, epithelialization and scarring [14]. The content of vitamin A was 0.52±0.33, 0.36±0.34 and 0.38±0.35 μg/ml, respectively (p=0.0045). There were no differences in the content of other fat-soluble vitamins.

Parameters of clinical blood test were similar. The most homogeneous distributions were observed for lymphocytes, neutrophils and eosinophils (p>0.4592).

The most significant differences between patients with different types of wound healing were found for carbohydrate metabolism parameters **(Table 1)**.

There were significant differences in HOMA-IR insulin resistance index between groups 1 and 3 (4.50±1.84, 2.50±1.76 and 1.30±0.91, respectively, p<0.0001).

We found significant differences for serum insulin between groups 1 and 3 (18.80±5.52, 10.60±2.31 and 5.30±0.47 mIU/l, respectively, p<0.0001).

According to modern literature data, insulin resistance and hyperinsulinemia without previous type 2 diabetes mellitus are currently considered as ones of the factors of poor postoperative outcomes [5].

Table 2 presents the results of univariate logistic regression analysis of various risk factors of complicated and delayed wound healing.

Risk of complicated and delayed wound healing is increased from 48.4% to 100.0% under these factors. At the same time, the most informative predictors of unfavorable healing of postoperative wound (risk 87.5—100.0%) are three factors (insulin resistance index ⩾3.1, insulin ⩾14.0 mIU/l and IL-1β (spontaneous release) ⩾45.0 pg/ml) **(Fig. 1—3)**.

Importantly, the content of pro-inflammatory cytokines decreases in case of physiological course of wound healing. However, long-standing wounds are accompanied by elevated levels of pro-inflammatory cytokines [12].

Table 1. **Quantitative indicators of carbohydrate metabolism**

Variable	Group			*p-value*
	1 (*n*=21)	2 (*n*=16)	3 (*n*=12)	
Insulin, mIU/l	18.80* [16.30; 23.40]	10.60 [8.15; 11.80]	5.30 [4.72; 5.70]	<0.0001*
Glucose, mmol/l	5.50 [4.90; 5.90]	5.30 [4.88; 5.55]	5.30 [5.05; 5.55]	0.435
Insulin resistance index HOMA-IR	4.50* [4.10; 5.10]	2.50 [2.25; 2.70]	1.30 [1.12; 1.42]	<0.0001*

Note. data are presented as median and interquartile range (Me [Q25; Q75]); * — significant differences (p<0.05).

Table 2. **Key factors affecting the risk of complicated and delayed wound healing**

No.	Factor	Absolute risk (%)		Risk bias (95% CI)	Relative risk (95% CI)	*p-value*
		Factor –	Factor +			
1	Insulin resistance index ⩾3.1	0* (0.0%)	21 (100.0%)	100.0	—	<0.0001*
2	Insulin ⩾14.0 mIU/l	2* (6.9%)	19 (95.0%)	88.1 (74.8; 101.4)%	13.78 (3.60; 52.66)	<0.0001*
3	IL-1β (spontaneous release) ⩾45.0 pg/ml	14* (34.1%)	7 (87.5%)	53.4 (26.2; 80.5)%	2.56 (1.56; 4.22)	0.005*
4	Glucose ⩾5.4 mmol/l	7 (30.4%)	14 (53.8%)	23.4 (–3.4; 50.3)%	1.77 (0.87; 3.61)	0.098
5	White blood cell ⩾5.2·109/L	6 (30.0%)	15 (51.7%)	21.7 (–5.4; 48.8)%	1.72 (0.81; 3.67)	0.131
6	Vitamin D ⩾32.4 ng/ml	11 (35.5%)	10 (55.6%)	20.1 (–8.4; 48.5)%	1.57 (0.83; 2.94)	0.171
7	IL-8 ⩾11.0 pg / ml	12 (37.5%)	9 (52.9%)	15.4 (–13.6; 44.5)%	1.41 (0.75; 2.66)	0.299
8	TNF-α (induced release) <2 084.0 pg/ml	6 (33.3%)	15 (48.4%)	15.1 (–12.9; 43.0)%	1.45 (0.69; 3.07)	0.305
9	Vitamin K ⩾1.3 ng/ml	14 (38.9%)	7 (53.8%)	15.0 (–16.5; 46.4)%	1.38 (0.72; 2.65)	0.350
10	Serum TNF-α <1.0 pg/ml	16 (40.0%)	5 (55.6%)	15.6 (–20.3; 51.4)%	1.39 (0.69; 2.79)	0.394
11	Serum IL-1β ⩾11.0 pg/ml	17 (40.5%)	4 (57.1%)	16.7 (–22.9; 56.2)%	1.41 (0.67; 2.96)	0.409
12	TNF-α (spontaneous release) ⩾1.0 pg/ml	4 (50.0%)	17 (41.5%)	–8.5 (–46.3; 29.3)%	0.83 (0.38; 1.81)	0.655

Note. * — significant differences ($p<0.05$); 95% CI — 95% confidence interval.

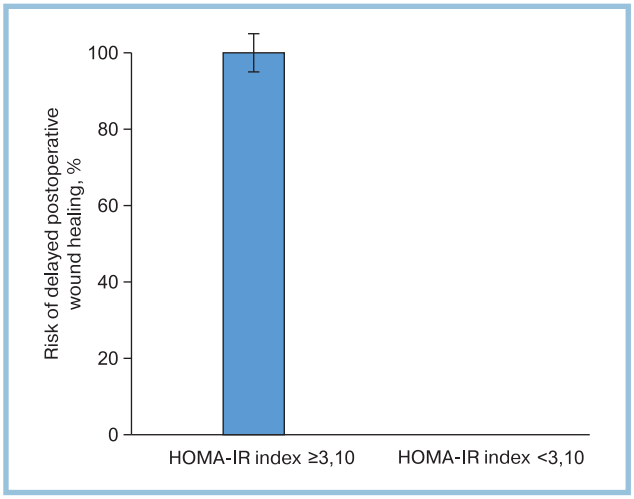


Fig. 1. **Risk (%) of delayed postoperative wound healing depending on HOMA-IR insulin resistance index.**

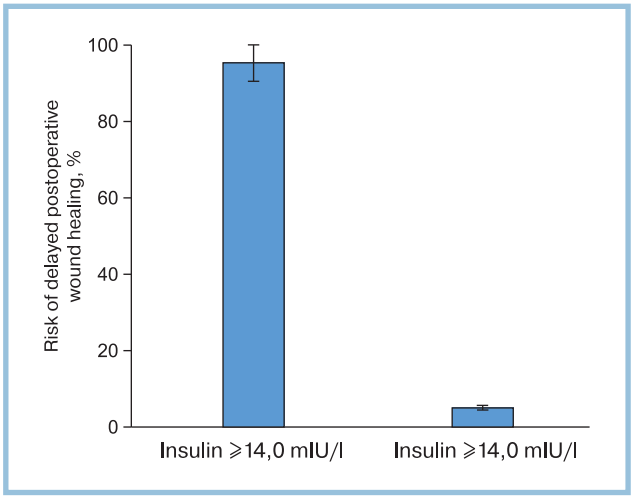


Fig. 2. **Risk (%) of delayed postoperative wound healing depending on serum insulin.**

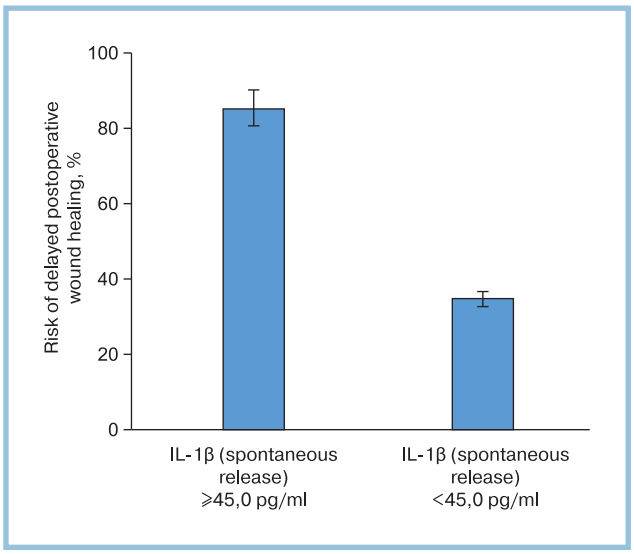


Fig. 3. **Risk (%) of delayed postoperative wound healing depending on serum IL-1β (spontaneous release).**

Conclusion

Predictors of complicated and delayed wound healing with risk increment from 87.5 to 100.0% in overweight patients seeking for aesthetic contouring of the mammary glands and anterior abdominal wall are insulin resistance index ⩾3.1, insulin ⩾14.0 mIU/L and IL-1β (spontaneous release) ⩾45.0 pg/mL. Identification of these factors in preoperative period will make it possible to predict unfavorable course of wound process and determine treatment strategy.

Author contribution:
Concept and design of the study – E.P. Sukhoparova, I.E. Khrustaleva, E.V. Zinovev
Collection and analysis of data – E.P. Sukhoparova
Statistical analysis – E.P. Sukhoparova
Writing the text – E.P. Sukhoparova
Editing – I.E. Khrustaleva, E.V. Zinovev

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