EPMA Journal (2017) 8:23–33
DOI 10.1007/s13167-017-0081-y

REVIEW

Impaired wound healing: facts and hypotheses for multi-professional considerations in predictive, preventive and personalised medicine

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Received: 19 January 2017 / Accepted: 29 January 2017 / Published online: 3 March 2017

Abstract Whereas the physiologic wound healing (WH) successfully proceeds through the clearly defined sequence of the individual phases of wound healing, chronic non-healing wounds/ulcers fail to complete the individual stages and the entire healing process. There are many risk factors both modifiable (such as stress, smoking, inappropriate alcohol consumption, malnutrition, obesity, diabetes, cardio-vascular disease, etc.) and non-modifiable (such as genetic diseases and ageing) strongly contributing to the impaired WH. Current statistics demonstrate that both categories are increasingly presented in the populations, which causes dramatic socio-economic burden to the healthcare sector and society at large. Consequently, innovative concepts by predictive, preventive and personalised medicine are crucial to be implemented in the area. Individual risk factors, causality, functional interrelationships, molecular signature, predictive diagnosis, and primary and secondary prevention are thoroughly analysed followed by the expert recommendations in this paper.

Keywords Predictive preventive personalised medicine · Wound · Impaired healing · Diabetes · Cardio-vascular disease · Cancer · Flammer syndrome

Introduction

A physiologic wound healing is a highly orchestrated process initiated by the tissue injury and resolved by the restoration of tissue integrity. It involves several overlapping phases: hemostasis, inflammation, proliferation, and remodeling [1]. Immediately after injury, the hemostasis phase is triggered, accompanied by immediate vascular contraction, platelet aggregation, and fibrin clot formation, which altogether initiate the next phase, namely the inflammatory one. During this phase, the platelets get activated, and the injured tissue releases a well-controlled panel of growth factors, cytokines, and chemoattractants which, in turn, do attract neutrophils, macrophages, and lymphocytes to the wound site. The locally involved extracellular matrix (ECM) and the entire wound area get enriched by the recruited platelets, macrophages, and bone marrow-derived stem cells which altogether release the core of growth factors promoting fibroblast activation and initiating the next phase - the proliferative one. Fibroblasts migrate into the wound area and proliferate almost simultaneously with endothelial cells triggering revascularisation by de novo capillary growth within the wound area. The fibroblasts secrete the essential molecular repertoire used to build up new ECM including collagen, glycosaminoglycans, and proteoglycans and launch the final remodelling phase of the wound healing. During this phase, an extensive qualitative and quantitative remodelling of ECM and local vascular system occurs by strictly regulated matrix metalloproteinases (MMPs)/ tissue inhibitor of metalloproteinase (TIMPs) complexes. This phase is a long-term process persisting over months and even years depending on the wound characteristics and individual health condition of the patient [1–3].

Whereas the physiologic wound healing successfully proceeds through the clearly defined sequence of the individual phases described above, chronic (non-healing) wounds/ulcers fail to complete some individual stages and the entire healing process, and stagnate usually at the early inflammatory stage. Chronic wounds are defined as those which do not follow the normal healing process and show no signs of effective healing within 3 months after the tissue injury [4]. The features characteristic for the chronic

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wounds are prolonged or excessive inflammatory phase [5], over-abundant neutrophil infiltration [6], persistent infections [7], and frequent formation of tissue/organ atypical biofilms [8, 9].

Substantial socio-economical consequences caused by complex medical services dedicated specifically to the care needed for the chronic wounds negatively impact healthcare systems worldwide. In the USA alone, over 25 billion US $ are spent annually for the treatment of chronic wounds affecting around 6.5 million patients [10]. Problematic wound healing and chronic wounds may result from a broad spectrum of sub-optimal health conditions, severe pathologies and comorbidities predisposing the affected individuals and corresponding patient cohorts to hindered wound healing and consequent pathologic developments such as chronic inflammation, persistent infections, "open wounds", cancerogenous wound transformation, etc. This article provides deep analysis of the risk factors, causal interrelations, and consequences linked to impaired wound healing, in order to motivate multi-professional considerations and development of innovative medical and technological approaches focused on prediction, prevention, and personalised treatments in the field.

Risk factors contributing to non-physiologic and impaired wound healing

There is a great number of risk factors which individually and combined may predispose to impaired wound healing. Here, we have categorised them as non-modifiable (unpreventable) risk factors (part A) and modifiable (preventable) (part B) ones as presented below. Further, comorbidities (part C) and risks of infection (part D) known as strongly contributing to the delayed and impaired wound healing are analysed in the paper.

Non-modifiable risk factors

Genetic component as unpreventable risk factor of ineffective healing processes

As described above, wound healing is a complex process involving a number of key-pathways regulating the response of many gene panels. Therefore, the genetic component is a prominent contributor to the wound healing. Indeed, some inborn genetic diseases are known to lead to non-physiologic and impaired wound healing, e.g. in case of Down syndrome [11] and Ataxia-telangiectasia [12, 13]. Further, rare genetic diseases are known to be responsible for the occurrence of venous ulcers in about 10% of cases [14]. The associated genetic defects can involve mutations in individual genes or gene-clusters, chromosomal aberrations, etc. Those defects may lead to the clinical manifestation in disorders of the immune system, of haemoglobin synthesis, of vasculopathies, of connective tissue diseases, of progeroid syndromes, etc. [14]. Hence, chromosomal aberrations are known for "Klinefelter syndrome" characterised by the presence of an additional X-chromosome. In Klinefelter patients, the incidence of varicosis and thrombosis is significantly increased, and about 13% of these patients develop venous ulcers, due to a post-thrombotic syndrome caused by high levels of the fibrinolysis inhibitor PAI-1 and diminished fibrinolysis [14–16].

Further, disorders of the immune system are known risk factors of the impaired WH, due to their particular role in the inflammatory phase. Leukocyte adhesion deficiencies (LADs)—LAD-I is caused by a mutation of the gene encoding the β2 chain of the integrins. LAD II is caused by a genetic defect in the synthesis of fucosylated glycostructures resulting in the absence of functional selectin ligands. LAD III is caused by a genetic defect of the leukocyte integrin [14]. All the LADs result in decreased migration of neutrophils to the wounded tissue and lacking phagocytosis ability of neutrophils in the wound bed. These genetic defects increase the susceptibility of affected patients to infections and consequent risks of severe wound complications [17]. TAP deficiency syndrome is characterised by the reduced expression of HLA class I molecules on the cell surface. Consequently, patients demonstrate abundant bacterial infections of the respiratory tract and chronic granulomatous skin lesions possibly caused by cells bearing inhibitory HLA class I receptors, i.e. NK and γδ T cells [18].

The next group is disorders of haemoglobin synthesis. Sickle cell anaemia caused by a point mutation in the β-globin gene results in an abnormality of the haemoglobin protein responsible for sickle shaped erythrocytes [14]. The disease-characteristic sickle shape and reduced deformability of affected erythrocytes result in vascular occlusion of small vessels and subsequent necrotic and ischemic injury [19]. Consequently, any trauma happened to the lower extremities results in their ulceration in 10–70% of sickle cell anaemia patients [19, 20]. Further, in case of Thalassemia which is a quantitative disorder of haemoglobin synthesis, about 27% of the affected patients develop chronic ulcers [21] due to poor peripheral oxygenation resulting from the existing underlying haemolytic anaemia [22].

Another group is vasculopathies. About 40% of the etiologically unexplained thromboses occur due to mutations in genes involved specifically in the coagulation system [14]. MTHFR polymorphism caused by a mutation in the 5-MTHFR gene leads to a development of hyperhomocysteinaemia—well-acknowledged risk factor for arterial and venous thrombosis and venous ulcers [14]. Further, mutations in factor V gene lead to an enhanced risk of thrombosis, since an activated protein C fails to inactivate factor V [14]. Other less common coagulation defects include prothrombin mutations, protein C deficiency, protein S deficiency, and antithrombin deficiency [14].

Inborn genetic disorders causing a connective tissue disease such as the Ehlers-Danlos syndrome lead to impairments

in the remodelling phase of wound healing [23]. Furthermore, Progeroid syndromes such as Werner syndrome tend to generate skin ulcerations [24].

In addition to clinically manifested genetic diseases, polymorphisms in the WH relevant genes may also have a vital role in predisposing affected individuals to impaired wound healing and ulceration. For example, in ECM regulation, which is highly relevant in case of WH, a polymorphism in MMP and/or fibrinolytic system genes can lead to delayed and even impaired healing [25]. HFE and FPN1 gene functions are associated with increased iron efflux from macrophages and depending on the gene polymorphism can strongly affect the efficiency of the fibrinolytic system. The C282Y variant HFE gene polymorphism has been demonstrated to increase the risk of developing venous leg ulcers by almost 7 times [26]. The FPN1 polymorphism 8CG also increases leg ulcer susceptibility [27]. The MMP-12 gene polymorphism -82AG has been proposed as a prognostic marker for venous leg ulceration progression [27]. Different FXIII polymorphisms have also been shown to modulate and even have protective effects against ulcers progression [25]. Similarly, the SNP-1562C/T detected in the MMP-9 gene, which downregulates MMP-9 expression, has been shown to have a protective effect against pressure ulcers [28].

Autoimmune diseases deteriorate the physiologic wound healing processes

Patients suffering from immune diseases have significantly larger wounds and their time to heal is much more prolonged compared to the general population [29]. Leg ulcerations have been monitored in several autoimmune diseases, especially in those linked to connective tissue pathologies. The highest rates of ulceration are recorded for rheumatoid arthritis and systemic lupus erythematosus. However, ulcerations were also seen in primary antiphospholipid syndrome and other autoimmune diseases [30].

Patients with rheumatoid arthritis are predisposed to develop chronic leg ulcers [31]. Foot ulcerations in rheumatoid arthritis are frequently recurrent, and the significantly extended time needed for them to heal, further, increases the risk of infections [32]. The aetiology of the ulcers was found to be multifactorial with the most common factors being venous insufficiency, trauma or pressure, arterial insufficiency, and vasculitis [33].

Modelling systemic lupus erythematosus by lupus prone mice revealed impairments in the inflammation phase and accelerated angiogenesis, which deeply impact the overall wound healing [34]. Further studies have demonstrated that specifically the presence of antiphospholipid antibodies associated with thrombosis development strongly promotes the leg ulceration observed in autoimmune diseases. These antibodies were reported to be involved in the pathology of primary antiphospholipid syndrome, in systemic lupus erythematosus, and in rheumatoid arthritis [30].

Accelerate and advanced ageing is a risk factor for healing

Aged subpopulations frequently demonstrate chronic non-healing wounds, and their impaired WH is a major medical care issue [35]. Individuals experiencing accelerated ageing, for example, in the case of Down syndrome or progeroid syndromes are also at great risk for slowed down and impaired wound healing [11, 24]. There are evident alterations at any stage of the healing process in aged individuals. Hence, they demonstrate an altered inflammatory response characterised by sustained elevation of proinflammatory cytokines such as IL-6 and TNFα and by declined levels of growth factors. This combination leads to high levels of TGF-β that may play a role in transforming wounds from acute to chronic ones by inhibiting the reepithelialisation [35]. Accelerated and advanced ageing is also associated with slowed macrophage and T cell infiltration to the wound area and reduced macrophage function [36, 37]. Contextually, aged mice demonstrate severe neutrophils depletion shown to delay wound closure [38].

Disturbed microcirculation and hypoperfusion characteristic for ageing skin contributes to the impaired inflammatory response and hinders the physiologic angiogenic phase in the overall WH [39].

Another characteristic of the ageing skin is a strongly reduced ECM production and overexpressed MMPs, especially MMP-2 that collectively leads to impairments in the remodelling phase [40, 41].

Sex hormones have a role in the physiologic wound healing. Further, there are gender-dependent particularities in WH of aged individuals: healing of acute wounds in aged males is significantly slower compared to this in aged females, due to positive regulatory effects of oestrogen in the WH [42].

Lifestyle related modifiable risk factors

Psychological stress modulates healing processes

Psychological stress demonstrates strong modulating effects towards WH by influencing mood, behaviour, and health condition of the affected individual. Issue-dedicated studies demonstrated its adverse effects on wound healing [43, 44]. Stress reduces the levels of the pro-inflammatory cytokines IL-1β, IL-6, and TNFα at the wound site. It also reduces expression levels of cytokine IL-1α and chemoattractant IL-8 and, consequently, interferes with the well-regulated inflammatory phase of the physiologic wound healing [45–48]. Some of the detrimental effects of stress on WH may be due to

upregulated glucocorticoids suppressing immune cell proliferation and decreasing production of IL-1α, IL-1β, and TNFα cytokines at the wound site [49, 50]. Further, stress leads to dysregulation of MMP-9 and MMP-2 levels at the wound site [51–53]. Although indirectly, stress is frequently associated with harmful habits such as cigarette smoking, inappropriate alcohol consumption and imbalanced nutrition—each of them adversely affects physiologic wound healing as demonstrated in detail below [54, 55].

Smoking strongly impairs wound healing

Smoking demonstrates detrimental effects on physiologic wound healing. Amongst over 4000 substances detected in tobacco smoke, several ones negatively impact healing processes [56]. To this end, nicotine strongly promotes vasoconstriction leading to disturbed microcirculation that negatively impacts WH [56, 57]. Further, smoking attenuates the inflammation phase by impairing white blood cell migration, reducing neutrophil bactericidal activity, and depressing IL-1 production [56, 58]. The proliferative phase is impaired by the reduced fibroblast migration and proliferation in addition to the downregulated collagen synthesis and deposition in smokers [56, 58]. Additionally, smoking disrupts epithelial regeneration and normal angiogenesis and decreases ECM production [56]. Overall, smokers show delayed wound healing, increased frequency of wound healing complications and wound dehiscence compared to non-smokers [56, 59, 60].

Inappropriate alcohol consumption is linked to non-physiologic healing processes

Moderate alcohol consumption demonstrates some protective effects against cardiovascular disease [61–63] which might be beneficial for WH as a whole. In contrast, inappropriate alcohol consumption may have strong adverse effects on an individual response towards an acute and chronic injury. Alcohol has been shown to play a role of immunomodulatory agent: acute alcohol consumption has inhibitory effects on the release of pro-inflammatory cytokines, while chronic alcohol consumption lead to a significantly prolonged response of inflammatory cells [64]. In experimental models, binge drinking before trauma resulted in attenuated levels of TNFα, IL-1, and IL-6 [65]. In human alcoholics, the levels of the immunosuppressive cytokine IL-10 were significantly increased over those in non-alcoholic individuals after major surgical intervention [66]. Alcohol consumption is also linked to the reduced T cell proliferation capacity important for the physiologic WH [67, 68]. Relevant murine models demonstrate that acute alcohol consumption decreases the expression of VEGF receptors and reduces nuclear expression of HIF-1α in endothelial cells, thereby affecting angiogenesis and the proliferative phase of wound healing [69, 70]. There are also studies showing that inappropriate alcohol consumption has an adverse effect on the physiologic reepithelialisation and collagen production [69–72].

Imbalanced diet is critical for the physiologic wound healing

An optimal setup of nutrients is extremely important for the regulation of all individual phases of wound healing and for the entire capacity of the body to perform the wound healing process successfully. Both deviations from the physiologic body mass index (BMI), namely too high as well as too low body BMI may predispose an individual to delayed and even impaired wound healing. The detailed analysis of the issue is provided below.

Malnutrition The need for cell proliferation and protein synthesis during the wound healing process increases the body's nutritional needs [73, 74]. Consequently, deficiencies or depletions in carbohydrates, protein, fatty acids, vitamins, or micronutrients may lead to impaired wound healing [75]. In particular, carbohydrates are needed to supply energy for the healing process and have been shown to be the key factor for activating several enzymatic complexes essential for the wound repair [76–79]. Certain amino acids, specifically leucine, glutamine, and arginine, possess anabolic activity required for the healing process. Moreover, protein deficiencies decrease leukocyte phagocytosis and increase susceptibility to infection [80, 81]. Fatty acids are required to provide additional sources for the highly required energy; they act as signalling molecules and contribute to the inflammatory process and cell proliferation [80]. Micronutrients such as zinc and vitamins B and C act as essential cofactors for energy production and protein synthesis, and demonstrate antioxidant properties. Regarding the aged individuals who are at higher risk for impaired WH as described above, they require 50% more protein compared to young individuals and thus are more prone to suffer from protein deficiencies [80].

Obesity In 2014, 39% of adults aged 18+ worldwide were recorded as being overweight and 13% as being obese. Thus, worldwide nearly two billion adults are overweight and, of these, more than half a billion are obese [82]. Obese individuals have been demonstrated as being predisposed to several severe pathologies including impaired wound healing [76], which might be explained by hypoperfusion and ischemic effects that occurs in subcutaneous adipose tissue. Thus, if the tissue in the vicinity of the wound is inadequately oxygenated, the oxygen strongly dependent cellular repair processes do not take place adequately [83, 84]. Hypovascularity frequently observed in obese individuals, further contributes to poor perfusion and increases the risk of infections, due to a decreased infiltration of immune cells to the wound area [83, 85]. In addition, obese individuals frequently demonstrate

increased tension on the wound edges contributing to the wound dehiscence [76, 86]. Consequently, the pathogenic bacteria which thrive in the moist environment of skin folds have an ideal environment for invasion and tissue breakdown. Lastly, skin-on-skin contact causes friction that can lead to ulceration that are particularly frequent in obese individuals [76, 86, 87].

Pathologies/comorbidities

Diabetes mellitus and cascaded comorbidities: major issues in medical care of wounds

The global prevalence of diabetes has reached an epidemic scale by almost half of billion patients worldwide [82]; the prediction for the next decades is highly pessimistic. This reflects a dramatic increase in associated risk factors and severe comorbidities frequently linked to disturbed WH. Diabetic individuals demonstrate disturbances in all individual processes and healing stages that collectively lead to overall impaired healing of acute wounds and are prone to chronic non-healing wounds such as the diabetic foot ulcers. Rates of lower limb amputation in populations with diabetic history are up to 20 times higher compared to those in non-diabetic populations [82].

Diabetic patients demonstrate deficient neutrophil chemotaxis, phagocytic, and microbicidal activities contributing to the high susceptibility to infections [88–90]. Aberrant cellular infiltration [91], insufficient macrophage activation [92], decreased release of TNFα, IL-1β and VEGF from macrophages [93], and impaired leukocyte function [94] have been shown to negatively impact wound healing in diabetic individuals.

Fibroblasts from diabetic foot ulcers are characterised by strongly decreased proliferative response to growth factors [95] and impaired signalling resulting in a diminished formation of granulation tissue [96, 97].

Between 30 to 50% of diabetic patients suffer from peripheral neuropathy, which increases the risk of ulcer development and predisposes them to delayed cutaneous tissue repair [98–100]. In the diabetic condition, the entire core of neuropeptides is strongly dysregulated such as downregulated SP, NPY, CGRP and upregulated CRF, α-MSH and NT. These neuropeptides play a key role in several stages of WH acting as chemoattractants, modulating permeability of blood vessels, improving adhesion of leucocytes, regulating expression of cytokines, stimulating endothelial cell proliferation, and enhancing VEGF release. The overall altered neuropeptide expression leads to the dysregulation of the downstream cytokines in the skin that results in the impaired wound healing [101].

Excessive activation of MMP-2 and MMP-9 combined with persistent nitrosative and oxidative stress and with excessive formation of advanced glycation end-products leads to ECM instability and to the breakdown of essential matrix proteins and growth factors [102–105]. Diabetic individuals show delayed reepithelialisation [106] and altered sensitivity to VEGF resulting in decreased angiogenesis [107].

Lastly, diabetic patients are strongly predisposed to severe comorbidities each of them individually and collectively altogether are functionally linked to impaired wound healing as analysed below in detail.

Cardio-vascular disease is critical for WH and follow-up cascade of pathologies

In general, vascular diseases resulting in local and/or systemic ischemic effects strongly affect healing processes, due to undersupplied oxygen and diminished levels of essential nutrients delivered to the tissue. Chronic non-healing wounds developed in the lower limbs is the typical complication of advanced diabetes as described above. Cardiac component plays a role as well. Hence, it has been shown that heart failure is predictive for the delayed healing of diabetic foot ulcers being strongly associated with poor prognosis [108, 109]. Further, heart failure is an independent risk factor for venous leg ulcers [110].

From a statistical viewpoint, venous ulcers alone affect up to 2.5 million patients annually in the USA for example, severely diminishing the patients' quality of life and negatively impacting medical care as a whole [111]. However, early/predictive diagnosis followed by timely prevention may help corresponding patient cohorts to avoid severe complications linked to impaired WH. For example, critical limb ischemia (CLI) is characterised by non-healing ulcerations [112]. However, well-targeted preventive procedures such as endovascular revascularisation capable of restoring the blood supply to the tissue have been shown to be effective for improving the wound healing quality [113].

Another example of impaired wound healing is provided by venous ulceration. The exact mechanism underlying this pathology is not well understood yet; however, venous hypertension resulting from venous reflux is assumed to be the main cause of the disease and its complications [111]. These wounds, if become persistent, have been reported as leading to malignant transformation of the chronic leg ulcers providing, therefore, the clear functional link for the cascade of pathologies developed in a clear sequence, namely, untreated persistent vascular disease resulting in the chronic non-healing wounds finishing with aggressive cancer development at the wound site [114–116].

Cancer and impaired wound healing: multi-faceted interrelationships

Wound healing on one side and tumour pathologies on the other side are two areas which are characterised by multi-

faceted interrelationships with each other as well as with other highly relevant medical areas already mentioned above. Herewith we provide some examples for the multifunctional links strongly supported by independent studies, available data and literature sources:

1. Chronic non-healing wounds—high risk of cancerous transformation of the affected tissue [114–123]
2. Relevant genetic diseases (e.g. Down syndrome)—increased stress (excessive production of SOD_2)—insufficient repair processes—strong predisposition to impaired wound healing and cancer [11, 124, 125]
3. Malnutrition—non-physiologically low BMI—impaired wound healing and poor prognosis in metastatic disease [80, 126]
4. Obesity—risk of diabetes—risk of chronic CVD—strong predisposition to chronic non-healing wounds and cancer [76, 127, 128]
5. Systemic hypoxia—impaired wound healing and strong predisposition to aggressive metastatic disease [75, 129]
6. Chronic inflammatory processes—chronic non-healing wounds stagnating at the early inflammatory phase but not progressing into the later phases of healing—increased risks of cancer by chronic inflammation [130]
7. Autoimmune diseases—strong predisposition to impaired wound healing and cancer [29, 131]
8. At the molecular level, non-physiologically upregulated activities of metalloproteinases (in particular MMP-2 and MMP-9) and dysregulated enzymatic complexes MMPs/TIMPs are characteristic for both impaired wound healing and aggressive tumour promotion and metastatic disease [132, 133]

All the cascades listed above demand broad attention at the levels of fundamental research and complex healthcare approaches.

The causality between the WH and cancer has been demonstrated to be both sided:

- Chronic non-healing wounds may lead to the cancer development [114–123]; some authors characterise tumours as "wounds which do not heal" [134].
- Cancer patients frequently demonstrate delayed and impaired wound healing; these impairments diminish treatment success and contribute to aggressive metastatic disease [130, 135]
- Wound healing and cancer development share common cellular and molecular mechanisms [136]

Contextually, independent studies indicate that the wound healing environment provides an opportunistic matrix for tumour growth [137, 138]. For instance, human basal cell carcinoma has been observed in areas of wound healing, including sites of vaccination [117, 118], surgery [119, 120], burns [121], and trauma [122, 123]. Modelling of breast cancer in mice has demonstrated that wounding next to the tumour significantly increases tumour size, and injecting the wound fluid closely to the tumour site results in strongly promoted tumour growth [139]. Additionally, acute inflammation triggered by a biopsy in mammary mouse model was shown to enhance the risk of developing peripheral metastases. This is probably due the inflammation in the primary tumours and in targeted organs, favouring the seeding of released tumour cells [140].

The presence of tumor appears to inhibit wound healing in cutaneous wounds [141]. In consensus, a small sample size study registered higher rates of non-healing wounds in patients with cancer [142]. Another study examined the cellular and molecular alterations of the dermal wound healing process in rats bearing oral carcinoma. On a macroscopic level, reduced rates of wound closure have been demonstrated compared to the tumour-free controls. On a microscopic level, enhanced numbers of immature macrophages in the wound area have been detected demonstrating adverse effects on the healing. In the tumour bearing mice reduced maturation of those macrophage have been seen, which negatively impacts the inflammatory processes of wound healing. Tumours reduce expression levels of the immunomodulatory genes *Tlr4*, *IL-1β*, *Ccl2*, *IL-10*, *Ccl3*, and *Cxcl1*, which are essential for physiologic wound healing. Taken the above summarised data together, it is evident that, in particular, the physiologic recruitment of the immune cells and the initiation and resolution of the inflammatory response are suppressed in the presence of a tumour contributing to the impairments of wound healing [143].

In addition to the molecular and cellular mechanisms linked to the primary tumour development, impaired wound healing in cancer patients may secondary result from the systemic toxic effects of anti-cancer treatments such as irradiation and chemotherapy [126]. Finally, in most studies approximately 40 to 80% of patients with cancer are presented as malnourished, which increases their susceptibility to infection and overall tendency to delayed wound healing [126]. To this end, please see the subchapter "Infection" provided below.

Infection impairs healing processes of the host

Infection to the wound is an extrinsic factor strongly retarding healing processes. Live bacteria and bacterial toxins—both lead to a strong upregulation and prolonged activity of pro-inflammatory cytokines, excessive inflammatory responses and damage to the affected tissue. In turn, the recruited inflammatory cells as well as invaded bacteria themselves contribute to the overexpression of matrix metalloproteases degrading the ECM and growth factors overloading the wound bed [75, 144]. Some

pathologies such as diabetes mellitus are known to increase risks of chronic infections, due to synergic effects of ineffective immune response on one side and on the other side systemic oxygen undersupply—both dramatically increasing the risks of infection [145, 146].

Pathogenic bacteria colonising chronic wounds often form biofilms consisting of the aggregated bacteria embedded in a self-secreted extracellular polysaccharide matrix. Those biofilms provide the hosted bacteria with highly protective environment making them more resistant against any antibiotic treatments [75, 144]. Formation of the bacterial films within the wound impairs key healing processes such as the inflammatory immune response, granulation tissue formation, and reepithelialisation of the host's injured tissue [147].

Concluding remarks, working hypotheses and expert recommendations

As mentioned above, predictive diagnostics and targeted prevention of pathologies negatively impacting wound healing might be the clue to the most effective approach against impaired wound healing in stratified patient groups e.g. within the primary and secondary prevention in diabetes care. Further, well-controlled physiologic wound healing is effective in protecting affected individuals against potential pathologies cascaded by chronic non-healing wounds such as a malignant transformation of the affected tissue at the wound site.

Additionally to both above summarised approaches, herewith, we would like to propose some new concepts for multiprofessional considerations. The first one strongly involves expertise and daily practice of general practitioners who might be in duty to put a particular attention to any delayed wound healing in their patient pools within the broad population. Well elaborated issue-dedicated questionnaires would be of great help for this group of professionals, in order to estimate potentially undiagnosed pathologies linked to impaired healing processes and even individual predisposition of the affected individual which can be diagnosed well in time. This approach is highly promising for an optimistic scenario by reconsidering currently applied reactive medical care and may lead to a great success by innovative screening programmes, if appropriately applied to the broad population.

Another innovative concept comprises a development of new research areas of great clinical utility of the knowledge accumulated regarding individuals in suboptimal health conditions who demonstrate some symptoms potentially relevant for impaired repair and healing processes. This kind of stratification may be of particular value for predictive diagnosis and targeted prevention within the young subpopulations. Herewith, we provide an example by so-called "Flammer Syndrome" for innovative research in the area.

Potential relevance of "Flammer syndrome" for altered wound healing: facts and hypotheses

Flammer syndrome (FS) describes a highly specific phenotype characterised by strongly pronounced sensitivity towards stress stimuli and primary vascular dysregulation accompanied by a cluster of the syndrome-typical symptoms and signs such as altered gene regulation, frequently decreased blood pressure and low BMI amongst others; FS is more prevalent in young women and academic professions [148]. FS-individuals are considered to comprise otherwise healthy subpopulations which, however, may be strongly predisposed to some severe pathologies [148]. In turn, patients being already affected by severe pathology may be strongly predisposed to particularly poor outcomes, if demonstrating symptoms of FS [149].

In FS individuals, plasma levels of endothelin-1 (ET-1) are moderately till strongly increased [148] resulting in insufficient vasodilatation or inappropriate vasoconstriction clinically established as systemic hypoxia with ischemic lesions described for several organs including life-important ones [150]. Systemic hypoxia and local ischemic lesions play an important regulatory role in repair processes leading to impairments in wound healing as discussed above in several subchapters. To this end, it is notable that the quality of repair processes in general and, in particular, this of wound healing has not been investigated in FS-affected individuals. However, there is a large number of direct and indirect indications which motivates the healing relevant research to be dedicated specifically to the FS affected individuals, namely

- Elevated ET-1 and systemic hypoxia typical for FS and detrimental for WH [75, 151]
- Retinal vein occlusion is frequently demonstrated by FS individuals [150]
- At the molecular level, repair processes are diminished and both MMP-2 and MMP-9 are highly activated in FS individuals as well as in FS-affected patients suffering from normal-tension glaucoma; consequently tissues remodelling is altered in this patient cohort [152, 153]
- Finally, FS may predispose cancer patients to both impaired wound healing and aggressive metastatic disease, due to systemic hypoxic effects and upregulation of MMPs as proposed by dedicated research [149, 154–156].

Acknowledgements The authors thank the Scholarship Programme of the German State of North Rhine-Westphalia for students from Israel which has supported the actual project by granting the study stay of Eden Avishai in the scientific group of Prof. Dr. Olga Golubnitschaja at the Radiological clinic, University of Bonn in Germany in the year 2016.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of informed consent Patients have not been involved in the study

Statement of human and animal rights No experiments have been performed including patients and/or animals.

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