The significance of mitochondrial efficiency in the regeneration and rate of healing when using dental implants

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_Case 1


Fig. 10

Case I_Female, 45-years old.

Maxilla

Fig. 1_OPG of the starting situation, generalised parodontitis.

Fig. 2_Clinical situation 4.5 weeks post extraction, after molecular biological treatment.

Fig. 3_Implant positioning, flapless after CT.

Fig. 4_Fixed provisionals, fitted immediately post-op.

Fig. 5_Definitive fixed reconstruction, fitted 1.5 weeks post-op.

Fig. 6_Optimal result, cosmetically and aesthetically.

Mandible

Fig.7_Implants positioning, falpless after CT.

Fig. 8_Fixed provisionals, fitted immediately post-op.

Fig. 9_Definitive fixed reconstruction, fitted 1.5 weeks post-op.

Fig. 10_Optimal result, cosmetically and aesthetically.

_The number of dental implant procedures is constantly increasing. As absolute implantology activities increase, so do the number of older and/or multimorbid patients. Undoubtedly, impaired wound healing is to be taken into account for these patients.

Yet this aspect is given little or no attention in spite of the optimization of surgical procedures—such as, for example, ultrasound and laser surgery, ozone therapy, bone regeneration using synthetic materials, equine collagen absorbable membranes, the use of minimally invasive methods, as well as three-dimensional OP-planning, simulation and, following on from that, flapless techniques, the improvements to the surface structure and design of implants.

The fundamental aim of those who administer surgical (implantological) treatment is to minimise the repercussions of all sorts of operative procedures, significantly reduce regeneration and healing time, noticeably improve general feeling of wellbeing after operative interventions and provide patients with a fixed tooth replacement (at the very least a provisional) at the end of their operation.

Fig. 1

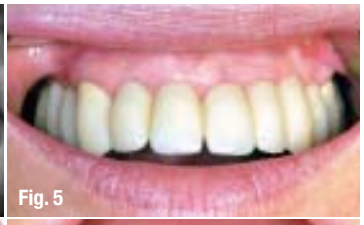
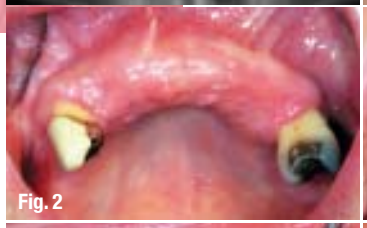


Fig. 5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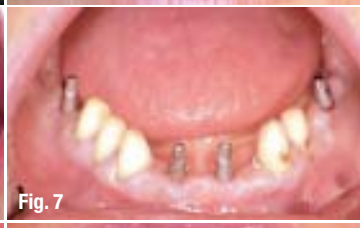
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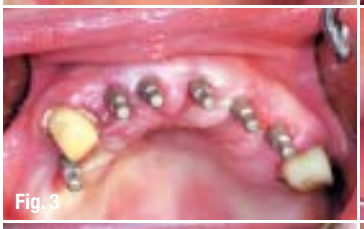


Fig. 3


Fig. 8

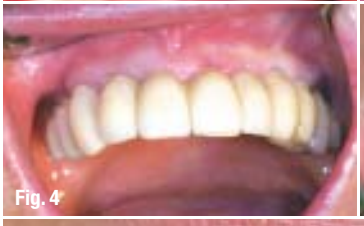


Fig. 4


Fig. 9


Fig. 6

The existing elaboration proves to be of outstanding significance in the functional capability of mitochondria to regeneration and the rate of healing. This is to show the persons administering (oral) surgical treatment that the operations protocol described here can be used simply and efficiently in everyday matters.

Meanwhile, within the realm of scientific knowledge it is clear that "oxidative stress" has a pivotal role to play in the aging process and in the development of chronic illnesses. Oxidative stress defines the imbalance between antioxidants and prooxidants, where the latter predominates.

Every organ and every tissue structure can be the target of an oxidative stress attack, which can lead to various illnesses such as atherosclerosis, diabetes, rheumatism and infectious illnesses, amongst others. Numerous studies have showed that an oxidative/antioxidative balance can delay the occurrence of illnesses and can even prevent them.

The question then arises as to whether purposeful diagnosis of oxidative/antioxidative status and individual molecular biological patient preparation to achieve an oxidative/antioxidative balance before and after the implant-op, is able to produce a sustainable reduction in the regeneration and healing phase.

Results

Included in the tests were 15 potential implant patients and 5 controls, who had no indication of periodontitis.

_Efficiency of antioxidative enzymes

The assessment of receptivity to oxidative stress in this study was made by determining different antioxidative effective enzymes. The body concentration of antioxidative/prooxidative molecules—such as NO, glutathione, ox-LDL-cholesterol, H_2O_2 and others—is influenced by genetic DNA variants of some enzymes, which radical and non-radical oxidants normally metabolise. Selected genetic variants of the relevant enzyme can involve partial or complete loss of function and also an increase in function.

Mitochondrial superoxiddisumtase-2 (SOD-2) and mitochondria nicotinamide-adenine-dinucleotide- phosphate (NADPH) oxidase have a central role to play in the defence of endogenously formed reactive oxygen species (in mitochondria). From the results it is apparent that each of the 15 potential implant patients included in the study possessed significant enzyme systems in one constellation, and this lead to an increased development of reactive oxygen species (ROS) in the mitochondria. Specifically, 93.3 % (n = 14) had limited functions in the NADPH oxidase complex (C242T), which protects against ROS. Of these, 71.4 % (n = 10) possessed SOD-2 in the functional form (16Ala), which lead to a further increase in ROS loading. ROS are not only formed endogenously, but also exogenously through cellular detoxification in the cytoplasma. Ionising radiation, UV rays, metals and harmful substances can intensify the formation of ROS. The defence of the exogenously formed ROS is also dependant upon several enzyme systems to which belong endothelial NO-synthase (eNOS) and glutathione S-transferase, types M1, T1 and P1 (GSTM1, GSTT1 and GSTP1).

_Case 2


Fig. 17

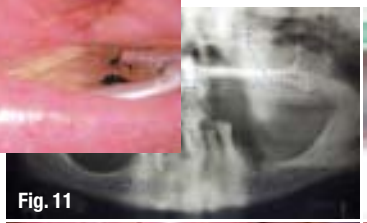
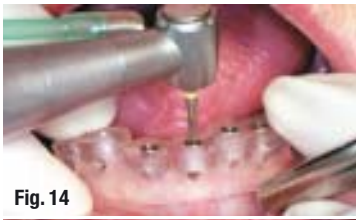


Fig. 11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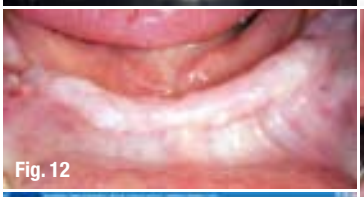


Fig. 12


Fig. 15


Fig. 13

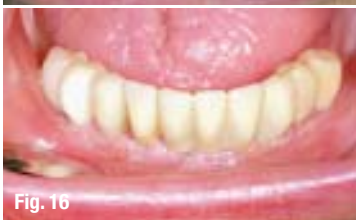


Fig. 16

Case II_Female, **76**-years old.

Fig. 11_OPG of the starting situation, generalized periodontitis.
Fig. 12_Clinical situation 4.5 weeks post extraction, after molecular biological treatment.
Fig. 13_Simulation after CT assessment.
Fig. 14–15_Implants positioning, falpless after CT using a template.
Fig. 16_Fixed provisionals, fitted immediately post-op.
Fig. 17_Definitive fixed reconstruction, fitted 2 weeks post-op, optimal result, cosmetically and aesthetically.

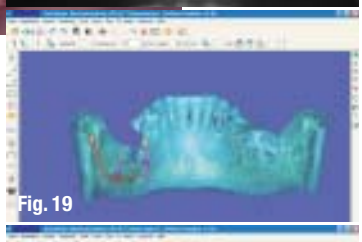
_Case 3


Fig. 25

Case III_Female, 49-years old

Fig. 18_OPG of starting situation, observe redundant bone quality.
Fig. 19–20_Simulation after CT-assessment for implants in regions 35 and 37.
Fig. 21_Differential diagnostic CT assessment to make up the template.
Fig. 22–23_Implant positioning, flapless, using template after molecular biological treatment.
Fig. 24_OPG of the implant positioning.
Fig. 25_Fixed provisional immediately postop.
Fig. 26_Definitive fixed reconstruction, fitted two weeks post-op, optimal result, cosmetically and aesthetically.

Fig. 18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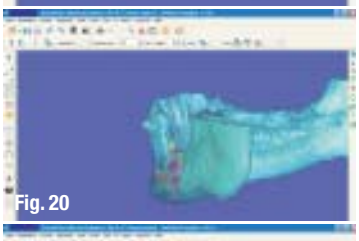
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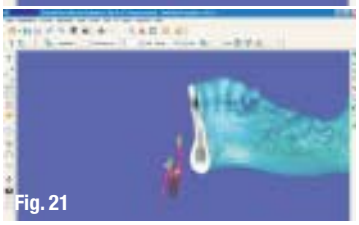
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Fig. 22

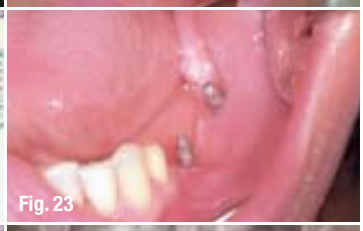
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Fig. 24

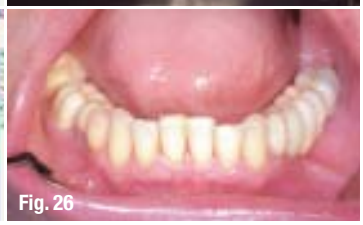
Fig. 26

Only 5 patients (33.33 %) had the enzymes GSTM1, GSTT1 and GSTP1 in their functional wild-type form. GSTM1/GSTT1 (deletions mutants) were completely lacking in 46.6/6.6 % of patients. In 11 patients, polymorphism existed either as a heterozygous (n=9) or homozygous characteristic (n=2), in the promotor of the eNO synthase gene T786C.

Infections can also be the cause of the formation of ROS. In 13 of the 15 patients, parodontogenic microorganisms, which cause acute and chronic infections, could be detected in the gingival pockets. The inflammatory reaction to a microbial stimulus is determined by variants in the interleukin-1 (polymorphisms at position -889 of human interleukin (IL)-1A-gene, to position +3953 of the human IL-1B-Gene) and interleukin-1-receptor gene (position +2018).

It is in this way that defined single nucleotide polymorphisms (SNPs) in these genes lead to soaring inflammatory reactions including increased production of ROS and, as a result, to destructive cellular processes with tissue damage. 80 % of the people examined had a genetic disposition to increased inflammatory reaction to infections and so have an increased quantity of ROS.

The results clearly show that potential implant patients have enzyme systems that have functional impairments, not being able to inactivate endogenously and exogenously formed ROS (Ill. 1).

_Damage by oxidative stress

Through the combined measurement of various biomarkers, exact details can be made about the cellular damage that has already occurred through oxidative stress, either endogenously or exogenously generated.

By measuring the oxidation products of lipids (ox-LDL; anti-ox-LDL- auto-antibodies), the destruction of vascular lipoproteins is defined, while measuring 8-hydroxy-guanosine (8-OHdG) shows the oxidative destruction inside the cells, ie, the genetic information. Oxidative destruction of proteins and enzymes reflects the identification of advanced oxidation protein products (AOPP). The abovementioned metabolites were measured in the patients' blood (plasma; serum) and urine.

It is clear from the results that all the potential implant patients who were examined already showed evidence of damaged lipoproteins (ox-LDL). Oxidised LDL has been proved to cause an induction of mitochondrial superoxide dismutase (SOD-2) and, in connection to it, the increased production of H_2O_2 leads to mitochondrial stress and, in the end, to a reduction in the function of immune effector cells (eg, macrophages) and cell death (apoptosis). The oxidative damage to intracellular structures, eg, to DNA and cellular proteins, was observed in 40 % of the patients.

These results clearly show that there is an imbalance between oxidative processes and antioxidative reserves. Oxidative stress has already lead to the accumulation of oxidative defects (Ill. 2).

Schedule 1

Ingredients MitoCur® HG
Coenzym Q 10
Carnosin
Alpha tocopherol acetate 50
Vitamin C
Taurin
Alpha-lipoic acid
Thiamine nitrate
Pyridoxin
Cyanocobalamin
N-Acetylcysteine
Methylsulfonylmethane (MSM)

Schedule 2

	Ox-LDL (U/L)*		Homocysteine (µmol/L)**		Thiole (µmol/L)***	
Patients	**Before**	**After**	**Before**	**After**	**Before**	**After**
P1	258.01	120	12.9	8.3	252.89	471.34
P2	179.64	80	17.4	8.5	203.43	389.23
P3	182.69	85	21.8	9.7	295.84	368.19
P4	166.41	95	13.1	9.7	194.12	338.82
P5	228.1	70	10.1	8.5	243.55	341.69

Normal ranges: * < 100 U/L; ** < 10 µmol/L; *** > 310 µmol/L

_The balance status of oxidants/antioxidants

Current oxidant/antioxidant status in the patients' serum was measured. In addition, oxidative effective peroxides, homocysteine and the antioxidative antagonists such as glutathione, SOD-2 and glutathione peroxidase and glutathione reductase were identified.

Along with peroxides, increased concentrations of homocysteine are toxic to cells. It is currently assumed that hyperhomocysteinemia leads to dysfunction and injury of the endothelial vessel, which results in thrombocyte activation and thrombosis activation. Damage to endothelial tissue is caused by reactive oxygen species.

The pathobiochemical potential of homocysteine should not be underestimated since this substance results at an important metabolism interface and accounts for disruptions to the entire methyl groups and sulphur metabolic groups. To the latter belong metabolites such as glutathione and taurine, which in turn have an important part to play in the framework of antioxidative protective systems.

In 4 patients (26.7 %), strongly increased peroxide loading was discernible, which can no longer be compensated for by a rise in antioxidative enzyme systems. Homocysteine levels in the patients examined were either within the range of limited conditions (n=4) or were clearly increased (n=11).

Among the 11 patients with seemingly normal peroxide mirroring in serum, 10 patients showed compensatorily increased activity of the antioxidative effective enzymes SOD-2, glutathione peroxidase and glutathione reductase. The concentrations of non-enzymatic antioxidants—eg, the proteinthioles and the glutathione—were clearly lowered in all patients. Tests of different working groups have shown that under mitochondrial stress—eg, from ox-LDL—the intracellular concentration of the mitochondrial H_2O_2 scavenger glutathione (GSH) was significantly decreased. With the results quoted above it has been clearly proved that visible signs of oxidative stress in all potential implant patients were exceedingly relevant.

_Status of the oxidant/antioxidant balance after treatment

In the following, 5 people with a moderate degree of antioxidative/oxidative imbalance were chosen and were subject to standardised, preoperative preparative procedures with MitoCur HG® (Adler Pharmacy, Niederfischbach, Germany), for a total period of four weeks.

The combination (Schedule 1) of substances and concentrations has been selected in such a way that deficiencies in antioxidative capacities can be balanced out. This is done by directly supplying antioxidants that are lacking and also by providing essential components for antioxidative effective enzyme systems (eg, SOD-2) and antioxidative effective molecules (eg, glutathione).

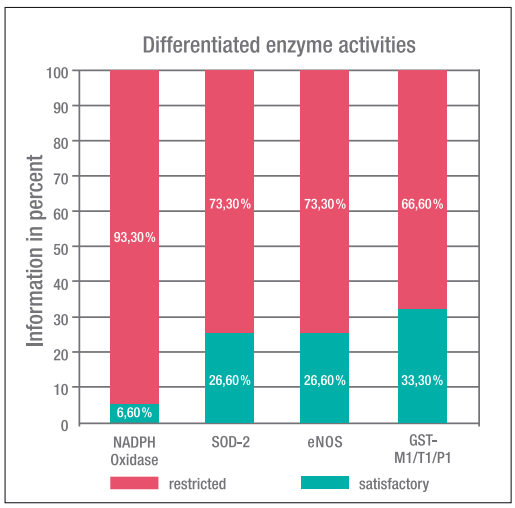

Illustration 1_Ability of antioxidative mitochondrial and non-mitochondrial enzyme systems to work in potential implant patients (n = 15).

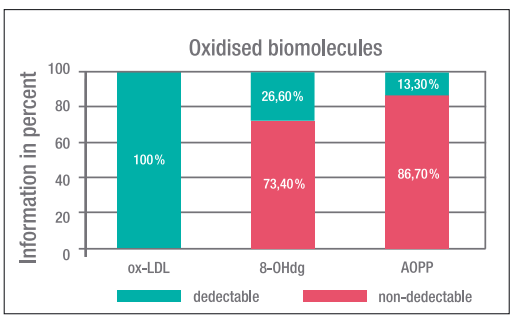

Illustration 2_Damaged biomolecules by oxidative stress (n = 15).

Afterwards the parameters ox-LDL, homocysteine and glutathione were selected as a biomarker for oxidative stress. All parameters can now be found in the reference section (Schedule 2).

Therefore, MitoCur HG® is able to restrict various switch points of oxidative stress and stabilise mitochondrial function.

_Summary

The examinations showed that, to varying degrees in all potential implant patients, biomolecules were changed by reactive oxygen species. Through relevant treatment methods, that is by taking MitoCur HG®, an oxidative/antioxidative balance can be once again established. The data and results established in the study verify the pathophysiology of disturbances to wound healing and clearly explain on a molecular level the significant reduction (60–80%) of regeneration and healing times in operative interventions. It is sustainable recommended that the operations protocol used in the study should be used as a standardised preoperative preparation procedure.

Minimally invasive operative handling after molecular biological preoperative management is shown in the following three clinical cases.

_Material and methods

_Homocysteine, Folic Acid and Vitamin B12 were determined with Immulite, from DPC Biermann (Bad Nauheim; Germany), according to the manufacturer's instructions.

_Substantiation of 8-OHdG is carried out quantitatively using a competitive in vitro ELISA test with monoclonal antibodies (Immundiagnostik AG, Bensheim, Germany).

_Substantiation of ox-LDL and anti-ox-LDL-autoantibodies was carried out quantitatively with a competitive in vitro ELISA-Test with monoclonal antibodies (Immundiagnostik AG, Bensheim, Germany).

_In determining peroxides, total lipid- and hydroperoxides were measured (Immundiagnostik AG, Bensheim, Germany).

_To determine total antioxidative capacity in serum, photometric ELISA method in EDTA-plasma was carried out and a fasting venous blood sample used (Immundiagnostik AG, Bensheim, Germany).

Genotyping was carried out according to molecularbiological standard procedures (eg, PCR, sequencing; pyrosequencing) and as stated in the instructions.

The literature list can be requested from the author.

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