Morphological and Biochemical Process Changes in Coronary Arteries of Diabetic Patients

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Abstract

Diabetes mellitus is a group of metabolic disorders in which a person suffers from elevated blood sugar levels, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is being produced. Elevated levels of blood sugar in diabetic patients lead to a series of complications. These can be divided into acute and chronic, which are further categorized as non-vascular and vascular. The latter are a consequence of changes in the biochemical processes that occur in the vessel wall. These biochemical processes are based on four independent biochemical abnormalities:

1) increased polyol pathway flux,
2) increased formation of advanced glycation end products (AGEs),
3) activation of protein kinase C (PKC) and
4) increased hexosamine pathway flux.

Independently or in combination, these processes lead to excessive production of free radicals from oxygen metabolism in mitochondria. The glucose-mediated increase of free-radical production and/or the reduction of antioxidant capacity cause changes in oxidative stress, thus changing tissue susceptibility to cell damage.

Such a string of phenomena can lead to a closure of a coronary artery segment, which results in the infarction of the heart muscle in the area supplied by this coronary artery. Since cardiac infarction is the most common cause of death in diabetic patients, understanding and researching diabetic angiopathy is of great importance.

Introduction

Coronary arteries and veins are responsible for the blood supply of the heart muscle. Arteries transport oxygen and nutrients either by diffusion or directly from the heart cavities via small vessels (1,2). Coronary arteries supply both ventricles and atria. When describing the arterial coronary system, the terms 'right' or 'left dominance' are used. The dominance is set according to the coronary artery that supplies the r. interventricularis posterior. The most common form is right dominance, while left dominance is found in approximately 10% of cases. In 15% of cases, the two arteries are co-dominant, i.e. they both supply the r. interventricularis posterior (1).

The right coronary artery originates from the right aortic sinus (sinus aortae Valsalvae dexter) and courses in the atrioventricular (AV) groove between the right atrium and the right ventricle (Illustration 1). In roughly 60% of subjects, its first branch is the r. nodi sinuatrialis, which supplies the sinuatrial (SA) node (1). At the right edge of the heart, it bifurcates for the second time, into the r. marginalis dexter, and continues down the coronary groove on the inferior (diaphragmatic) side of the heart. When it reaches the crux cordis (where the atrioventricular, interatrial and interventricular grooves meet), it branches into the r. nodi atrioventricularis, which supplies the AV node. An important branch of the right coronary artery is the r. interventricularis posterior, which travels in the bottom, i.e. posterior interventricular groove (sulcus) towards the apex of the heart, supplying both ventricles, as well as providing for the interventricular (IV) septum via its septal branches (rr. interventriculares septales). In some cases, it anastomoses with r. circumflexus and r. interventricularis anterior of the left coronary artery near the apex cordis (1,2).

The left coronary artery originates from the left aortic sinus (sinus aortae Valsalvae sinister) and flows in the coronary groove between the left auricle and the pulmonary trunk. In approximately 40% of subjects, the r. nodi sinuatrialis stems from the first part of the left coronary artery or from its circumflex branch (r. circumflexus) (1). At the beginning of the anterior interventricular sulcus (sulcus interventricularis anterior), the left coronary artery bifurcates into two branches: the left anterior descending artery or LAD (r. interventricularis anterior) and the left circumflex artery or LCX (r. circumflexus). The LAD runs in the anterior interventricular groove (sulcus interventricularis anterior) to the apex of the heart and supplies both ventricles and the interventricular septum via its
ventricular and septal branches. At the apex of the heart, it anastomoses with the r. interventricularis posterior of the right coronary artery (1,2). In most cases, the LAD branches into the r. lateralis, which descends down the front of the heart. Coursing in the coronary groove, the LCX stems into the r. marginalis on the left, pulmonary side of the heart and supplies the left ventricle. It then continues to the bottom side of the heart, where – in some instances – it anastomoses with the r. interventricularis posterior of the right coronary artery (1). Illustration 2 summarizes the origin and vascularization area of each coronary artery.

Morphology of vascular changes in diabetes

Diabetes mellitus is a syndrome reflected in digestive disorders and hyperglycaemia (high levels of blood sugar). It arises due to low levels of insulin or because of increased resistance to insulin, as well as the incapacity of the pancreas to produce adequate amounts of the hormone. The complications of the disease can be categorised into acute (e.g. diabetic ketoacidosis) and chronic, which are further classified into vascular and non-vascular (3). Vascular complications are divided into those relating to the large blood vessels and those appertaining to capillary malfunction in the target organs, i.e. macrovascular and microvascular angiopathy, respectively. Macrovascular angiopathy causes accelerated atherosclerosis, which can result in a myocardial infarction, cerebral infarction and gangrene of the lower extremities. Microvascular angiopathy mainly provokes small vessel defects in the retina, kidney and nervous system, i.e. diabetic retinopathy, nephropathy and peripheral neuropathy, respectively (4).

In most cases, angiopathies are brought about by fluctuations in blood sugar levels. Glycated haemoglobin (HbA1c) is the result of one-way non-enzymatic chemical binding of glucose to the protein chains of haemoglobin in erythrocytes. It reflects the average plasma glucose concentration and serves as a marker in determining the normality of blood sugar levels for the period between 4 weeks and 3 months. According to general consensus, normal blood sugar is indicated by levels of HbA1c under 7.0% (3).

Blood sugar levels have an important impact on the vascular system, namely accelerated atherosclerosis. With diabetes, the latter has a damaging effect on the aorta, as well as other large and medium-sized arteries. One of its typical ramifications is a higher degree of vascular issues at a younger age compared to subjects without diabetes. Myocardial infarction, which is caused by atherosclerosis of coronary vessels, is the most common cause of death in diabetics. The frequency according to gender is approximately the same (4). Damage to blood vessel walls due to high blood pressure (hypertension) is called hyaline arteriosclerosis. It manifests more often and in more acute form in diabetic patients than in other subjects. Nevertheless, this type of complication is not specific to diabetics, as it is also found in older patients without diabetes and/or hypertension (4).

One of the typical morphological changes in diabetics is the diffuse thickening of the basement membrane (microvascular angiopathy). Light or electronic microscopy can reveal the basal lamina, which separates the parenchyma or endothelial cells from the surrounding tissue. The basal lamina is discernibly thickened in the form of concentric layers of hyaline material, mostly made up from type IV collagen. Despite the thickening, capillaries in diabetics allow for more plasma proteins to pass through them than regular capillaries (4).

Vessel tissue damage in diabetics occurs on several levels. On the one side, hyperglycaemia precipitates acute, repeating changes in cell metabolism, while, on the other side, also having a long-term impact on stable macromolecules. Both phenomena contribute to vessel tissue damage. Other independent accelerating factors, such as hypertension and high blood fat, as well as the genetic susceptibility to vessel disease, must also be taken into account (Illustration 3).

Excessive blood sugar levels bring about an increase in cholesterol, which leads to atherosclerosis. Gradual buildup of atherosclerotic plaques on the inside walls of arteries can render these less flexible and progressively narrow their lumen (4,5).

Diabetic angiopathy causes the calcification of the tunica media in larger arteries, which principally hinders microcirculation. The thickening of the basement membrane is characteristic of diabetes and impedes normal microcirculation (6).

Vessel damage mechanism in diabetes

The connection between chronically high blood sugar levels and vessel damage is based on four independent biochemical irregularities: increased formation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), excessive activation of the polyol pathway and excessive activation of the hexosamine pathway (7).
In all four mechanisms, there is an excessive production of oxygen free radicals by the mitochondrial respiratory chain. The blood-sugar-induced increased generation of free radicals and/or the reduction of antioxidant capacity are the two main processes that influence changes relating to oxidative stress (7,8).

Production of advanced glycation end products (AGEs)

AGEs are the result of chain chemical reactions, which transpire after the initial non-enzymatic glycosylation or glycation (4,9). On extracellular components, e.g. collagen and laminin, the formation of AGEs triggers the cross-linking of polypeptides. If the cross-linking occurs between type I collagens, large arteries lose their elasticity, which makes them more susceptible to endothelial damage. As cross-linked extracellular proteins are resistant to proteolysis, there is both an increase in protein accumulation, as well as a reduction in their decomposition. At the same time, the cross-linked extracellular proteins lead to low-density lipoprotein (LDL) buildup, which in turn causes cholesterol accretion in the tunica intima. All of the above accelerates atherosclerosis (4,9).

The remaining AGEs bind with plasma proteins and restructure them in a manner that activates the transcription factor NF-κB in the nucleus, which subsequently prompts the production of various cytokines, growth factors and inflammatory molecules. Cytokines and growth factors are secreted by macrophages and mesangial cells (interleukin growth factor 1 (IL-GF-1), transforming growth factor beta (TGF-?), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF)). Coincidentally, the permeability of the endothelium is increased, the clotting capacity of blood rises and the formation of the extracellular matrix is accelerated (4,9).

Protein kinase C (PKC) activation

Elevated intracellular blood sugar levels set off the synthesis of diacylglycerol (DAG) and consequently the activation of PKC. This increases the activity of endothelin 1 – a potent vasoconstrictor – and reduces the activity of the endothelial nitric oxide synthase (eNOS) – a strong vasodilator. PKC influences the formation of the extracellular matrix, which is composed of profibrogenic molecules. TGF-? increases the formation of the extracellular matrix. PKC stimulates the formation of the procoagulative molecule PAI-1 (plasminogen activator inhibitor-1), which reduces fibrinolysis, while at the same time prompting an increased production of inflammatory cytokines in the vascular endothelium. Consequences of these phenomena include the constrictions of blood vessels, increased clotting and more intravascular inflammation, which gradually leads to small vessel blockage (4).

Intracellular hyperglycaemia induced by disruptions of the polyol pathway

Elevated blood sugar levels in the bloodstream lead to higher blood sugar levels in the tissues that do not require insulin to transport blood sugar through the cell membrane (nerves, lens, kidneys, blood vessels) as opposed to those that do necessitate glucose. Through the aldose reductase reaction, such blood sugar is first reduced to sorbitol, then polyol and finally fructose. The process involves the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), which acts as a cofactor. NADPH also acts as a cofactor with the glutathione reductase enzyme, which produces reduced glutathione (RG). RG serves as an important antioxidant mechanism in the cell; a drop in RG levels thus leads to oxidative stress. Persisting elevated levels of intracellular blood sugar lead to a reduction of NADPH, which is used by aldose reductase (the polyol pathway). This in turn decreases RG levels and increases the susceptibility of the cell to oxidative stress. The theorem can be proved by a simple test: if given an aldose reductase inhibitor, the subject’s diabetic neuropathy improves (4,10).

Increased activity of the hexosamin pathway

The fourth mechanism is tied to an elevated activation of the hexosamin pathway. When blood sugar levels within a cell are elevated, most of the blood sugar is metabolized through glycolysis and first reduced to glucose 6-phosphate, followed by fructose 6-phosphate and subsequent stages of the glycolysis process. Part of the formed fructose 6-phosphate does not continue down the glycolysis pathway, but instead enters one of the signalling pathways, where the glutamine-fructose-6-phosphate aminotransferase enzyme (GFAT) turns it into glucosamine-6-phosphate and finally to uridine diphosphate N-acetylgalactosamine. With the addition of the threonine and serine transcription factors, the latter increases the glycosylation of the SP-1 transcription factor, which increases its activity and leads to more phosphorylation. In this way, there is also an increase in PAI-1 and TGF-?1 transcription, which accelerates the pathological atherosclerosis of blood vessel walls by reducing profibrinolytic activity (10).

Conclusion

The location and extent of the infarction can be predicted by knowing the location of the occlusion, as well as by being familiar with the anatomy and supply...
system of individual coronary arteries. Illustration 4 shows an overview of the coronary vessels that are most frequently involved in myocardial infarction. In as much as 50% of cases, the infarction occurs due to blockage of the LAD branch (5). Consequently, the infarction spreads through the area supplied by the branch, i.e. the left and right ventricle and the interventricular septum (1,2). Such an infarction of the anterior wall can be supra-apical, antero-septal or apical. Approximately 30% of all infarctions happen due to blockage in the right coronary artery, which supplies the right atrium, the SA and AV nodes, as well as the posterior part of the interventricular septum (the infarction of the posterior wall can be postero-apical, postero-septal or postero-basal) (5). 20% of all the infarctions correspond to blockage in the LCX branch, which supplies the left atrium and the left ventricle (the infarction of the lateral wall can be apico-lateral or baso-lateral). Occlusions in other coronary vessels are statistically negligible (5). Good knowledge of the anatomy and the supply system of individual coronary arteries is essential in predicting the location and the extent of an infarction, if one knows the location of the occlusion. Understanding the mechanisms that exacerbate atherosclerosis helps us focus the research work on substances that influence and slow down the progress of coronary disease in diabetics, by affecting individual stages of those mechanisms.

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References

Illustrations

Illustration 1

Illustration 1 shows coronary arteries. The most common occlusion locations are numbered from 1 to 5.
Illustration 2

Illustration 2 shows individual coronary arteries, their origin, vascularisation area and how often occlusion of an individual coronary artery causes myocardial infarction (AV- atrioventricular, SA- sinuatrial, LAD- left anterior descending artery, LCX- left circumflex artery) (1,2,4,5).

<table>
<thead>
<tr>
<th>Artery/branch</th>
<th>Origin</th>
<th>Vascularization</th>
<th>Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>left coronary artery</td>
<td>sinus aortae Valsalvae sin.</td>
<td>majority of the left atrium and ventricle, interventricular septum, AV bundle, AV node</td>
<td></td>
</tr>
<tr>
<td>r. nodi sinuatrialis</td>
<td>r. circumflexus (a. coronaria sin.) in 40% of the population</td>
<td>left atrium in SA node</td>
<td></td>
</tr>
<tr>
<td>r. interventricularis ant. (LAD)</td>
<td>a. coronaria sin.</td>
<td>both atria, interventricular septum</td>
<td>50%</td>
</tr>
<tr>
<td>r. circumflexus (LCX)</td>
<td>a. coronaria sin.</td>
<td>left atrium and ventricle</td>
<td>20%</td>
</tr>
<tr>
<td>r. marginalis sin.</td>
<td>r. circumflexus (a. coronaria sin.)</td>
<td>left ventricle</td>
<td></td>
</tr>
<tr>
<td>right coronary artery</td>
<td>sinus aortae Valsalvae dext.</td>
<td>right atrium, SA and AV node, posterior part of interventricular septum</td>
<td>30%</td>
</tr>
<tr>
<td>r. nodi sinuatrialis</td>
<td>a. coronaria dext. (in 60% of the population)</td>
<td>SA node</td>
<td></td>
</tr>
<tr>
<td>r. marginalis dext.</td>
<td>a. coronaria dext.</td>
<td>right ventricle, apex cordis</td>
<td></td>
</tr>
<tr>
<td>r. interventricularis post.</td>
<td>a. coronaria dext.</td>
<td>both ventricles, interventricular septum</td>
<td></td>
</tr>
<tr>
<td>r. nodi atroventricularis</td>
<td>a. coronaria dext.</td>
<td>AV node</td>
<td></td>
</tr>
</tbody>
</table>
Illustration 3 shows causes and factors of diabetic tissue damage.
Illustration 4

Illustration 4 shows an overview of coronary vessels that are most frequently involved in myocardial infarction.

<table>
<thead>
<tr>
<th>Occluded artery</th>
<th>Infarction location</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>beginning of r. interventricularis ant.</td>
<td>anterior wall and apex cordis</td>
<td></td>
</tr>
<tr>
<td>middle or last part of r. interventricularis ant.</td>
<td>anterior wall supra-apical, antero-septal</td>
<td>50%</td>
</tr>
<tr>
<td>right coronary artery (a. coronaria dextra)</td>
<td>posterior wall postero-apical, postero-septal, postero-basal</td>
<td>30%</td>
</tr>
<tr>
<td>r. circumflexus</td>
<td>lateral wall apico-lateral, baso-lateral</td>
<td>20%</td>
</tr>
<tr>
<td>left and right r. interventricularis and r. circumflexus</td>
<td>anterior + posterior wall, interventricular septum</td>
<td>rare</td>
</tr>
</tbody>
</table>

**Illustration 4** shows most commonly affected coronary arteries in myocardial infarction, the location of arterial occlusion and typical infarction localization (1,2,4,5).
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