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TOPIC HIGHLIGHT

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Diabetic foot syndrome: Immune-inflammatory features as possible cardiovascular markers in diabetes

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Abstract

Diabetic foot ulcerations have been extensively reported as vascular complications of diabetes mellitus associated with a high degree of morbidity and mortality. Diabetic foot syndrome (DFS), as defined by the World Health Organization, is an "ulceration of the foot (distally from the ankle and including the ankle) associated with neuropathy and different grades of ischemia and infection". Pathogenic events able to cause diabetic foot ulcers are multifactorial. Among the commonest causes of this pathogenic pathway it's possible to consider peripheral neuropathy, foot deformity, abnormal foot pressures, abnormal joint mobility, trauma, peripheral artery disease. Several studies reported how diabetic patients show a higher mortality rate compared to patients without diabetes and in particular these studies under filled how cardiovascular mortality and morbidity is 2-4 times higher among patients affected by type 2 diabetes mellitus. This higher degree of cardiovascular morbidity has been explained as due to the observed higher prevalence of major cardiovascular risk factor, of asymptomatic findings of cardiovascular diseases, and of prevalence and incidence of cardiovascular and cerebrovascular events in diabetic patients with foot complications. In diabetes a fundamental pathogenic pathway of most of vascular complications has been reported as linked to a complex interplay of inflammatory, metabolic and procoagulant variables. These pathogenetic aspects have a direct interplay with an insulin resistance, subsequent obesity, diabetes, hypertension, prothrombotic state and blood lipid disorder. Involvement of inflammatory markers such as IL-6 plasma levels and resistin in diabetic subjects as reported by Tuttolomondo *et al* confirmed the pathogenetic issue of the a "adipo-vascular" axis that may contribute to cardiovascular risk in patients with type 2 diabetes. This "adipo-vascular axis" in patients with type 2 diabetes has been reported as characterized by lower plasma levels of adiponectin and higher plasma levels of interleukin-6 thus linking foot ulcers pathogenesis to microvascular and inflammatory events. The purpose of this review is to highlight the immune inflammatory features of DFS and its possible role as a marker of cardiovascular risk in diabetes patients and to focus the management of major complications related to diabetes such as infections and peripheral arteriopathy.

Key words: Diabetic foot syndrome; Inflammation; Cytokines; Cardiovascular risk; Marker

Core tip: An immune activation has been reported as important at several stages in the development of chronic wounds of diabetic foot syndrome (DFS). Immune-inflammatory up regulation may precede the incidence of DFS in the same way that it precedes some major cardiovascular diabetic complication such as coronary heart disease as reported by some studies that showed a significant negative correlation of adiponectin plasma levels with cardiovascular risk factors such as hypertension, dyslipidaemia and with previous cerebrovascular events such as previous transient *ischemic* attack/stroke and new onset events thus underlining the role of hypo-adiponectinaemia as a cardiovascular predictive factor in DFS.

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INTRODUCTION

Diabetes is a disease of metabolism clinically expressed by chronic hyperglycemia and blood lipid and protein disorders that have been extensively reported as linked to several complications that significantly impair the quality of life. Among diabetic vascular complications, foot ulcers represents the first cause of hospitalization in diabetics and a significant cause of health care costs (more than 20%-40% of health care resources have been reported as related to diabetes-related foot care)[1,2].

According World Health Organization, its' possible encompass all foot complications in the term diabetic foot syndrome (DFS) that has been defined as "ulceration of the foot (distally from the ankle and including the ankle) associated with neuropathy and different grades of ischemia and infection"[3]. More than 80000 amputations directly related to diabetes have been registrated in the United States annually[4] and the majority (80%) of these have been performed in patients with a previous foot ulceration[5]. These foot vascular complications represent a very common precursor event prior of lower extremity amputation among persons with diabetes[6,7]. Thus it explains that the foot ulcerations are considered as significantly predictive of morbidity, mortality, and disability.

It has been extimated that 15% of patients with diabetes will develop a lower extremity complication in their life[8]. Some authors reported a 0.5% to 3% incidence of diabetic foot ulcers[9], whereas foot ulcer prevalence, as reported by some population surveys, ranges from 2% to 10%[9]. A retrospective cohort study conducted in United States and enrolling more than 8000 patients with type 1 and type 2 diabetes showed that new cases of DFS were 5.8 % over an period of 3 years[10]. More than 15% of patients with DFS experienced a lower limb amputation and some authors reported that survival rate in patients that undertaken a lower limb amputation is significantly shorter and more than $ 2700 is the cost for a 2-year care of a new-diagnosed foot ulcer.

Foot ulcers have a complex and multifactorial pathogenesis with several causes working together to create pathogenetic pathway linked to foot ulceration onset in diabetic patients. Pathogenetic events able to cause diabetic foot ulcers are multifactorial. Among the commonest causes of these pathways it's possible to consider some triggers such as peripheral neuropathy, foot deformity, abnormal foot pressures, abnormal joint mobility, trauma, peripheral artery disease (PAD).

Peripheral neuropathy represents the most important cause in the pathway that causes foot ulceration in diabetic patients. Diabetic peripheral neuropathy (DPN) significantly impairs nerve activity throughout the body and can affect autonomic, motor, and sensory functions[11]. In sensory involvement the impairment of sensation that protects foot skin integrity makes the foot vulnerable to thraumatic damage caused by an excess of pressure, mechanical or thermal injury.

As reported by a recent study, sensory neuropathy represents the most frequent event in the patogenetic axis that causes ulceration in diabetic patients[12]. Other forms of neuropathy may also play a role in foot ulceration. Motor neuropathy impairs the balance of biomechanical forces, alter the integrity of foot anatomy by means foot deformities, impaired joint mobility and compromised loading of the extremities. These pathogenetic events impair mechanical forces balance during walking and induce a reactive thickening of skin (callus) and thus facilitating ischemic necrosis of tissues nearest to callus and leading to loss of skin and subcutaneous tissue integrity (breakdown) and to ulcers that represent the final step of this pathogenetic way.

Also autonomic neuropathy has a role in ulcer pathogenesis causing impairment and texture changes of skin integrity thus predisposing dryness and fissuring and opening potential entry for bacteria.

Another disorder that contributes to the development of foot ulcers is peripheral vascular disease that affects the blood vessels of small and large size. Both macro- and microvascular diseases are believed to contribute to the consequences of peripheral vascular disease, resulting in the inability of the ischemic limb to heal itself properly.

PAD has an increased incidence and prevalence in subjects with diabetes in relation of age and duration of disease. Hypertension, smoke habit, and lipid blood disorders are frequent comorbidities in diabetes with a well demonstred role in PAD pathogenesis. Studies have shown that peripheral vascular disease develops at a younger age among patients with diabetes as compared to the general population[13]. Ankle-brachial index (ABI), that originates by comparation of the systolic blood pressure at posterior tibial or dorsalis pedal level with brachial blood pressure, it's widely used to diagnose and evaluate severity of PAD. In patients with an ABI < 0.90, the relative risk has been

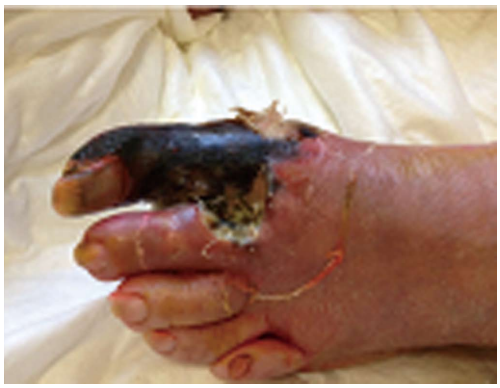

Figure 1 Infected diabetic foot ulcer. Tuttolomondo *et al*[21], personal data.

reported to be 1.25 (95%CI: 1.05, 1.47) for developing an ulcer *vs* diabetic patients with a normal ABI[14]. Lower limb ischaemia due to proximal arterial occlusive atherosclerosis is an important cause able to predispose to ulceration in more than 30% of cases[15]. Nevertheless a recent study reported that diabetic patients with PAD are more likely in comparison to non-diabetic subjects to have a distal occlusive arterial disease and an higher incidence of amputions and death related to cardiovascular causes[13].

An ischaemic diabetic foot appears as red, dry and with clinical findings suggestive of peripheral neuropathy and it also is susceptible to pressure damage by footwear.

Thus diabetic foot with ulceration is a complex problem resulting of the interplay of multiple pathogenetic noxae such as neuropathy, peripheral vascular disease, trauma and infections. Neuropathy and ischaemia may represent the first acting factors, most often together as neuroi-schaemia that is peripheral neuropathy and vascular disease in overlapping, whereas infection is mostly a super-infection.

It's possible to classify a diabetic foot in a pathophysiological and clinical way in: ischemic diabetic foot, neuropathic ischemic foot and infected diabetic foot, but this type of classification in clinical practice may appear too simple owing to the fact that it's possible to distinguish more frequent mixed clinical variants called neuro-ischemic diabetic foot. All these clinical variants of DFS have typical morphologic and clinical findings (Figures 1 and 2).

In this review, we will examine research articles with regard of involvement of immune-inflammatory markers in DFS and the role of DFS as a possible marker of cardiovascular risk in diabetic subjects.

CARDIOVASCULAR MORBIDITY IN PATIENTS WITH DFS

Diabetic patients show a poorer survival rate compared to patients without diabetes. Cardiovascular mortality and morbidity rates in diabetics have been reported by several studies as 2-4 times higher than in non-diabetic subjects. Different studies also indicate that foot ulcers in diabetic patients are linked to a higher mortality[13-17]. Furthermore diabetic foot represents an independent risk factor of morbidity in diabetic patients with a twice mortality rate

Table 1 Prevalence of previous cardiovascular events in patients with and without diabetic foot

	Pts with diabetic foot (n = 102) <	Pts without diabetic foot (n = 123)	P
CAD (%)	33 (32.3)	24 (19.5)	0.0043
TIA (%)	15 (14.7)	9 (7.3)	< 0.0001
Stroke (%)	18 (17.6)	11 (8.9)	< 0.05
Stroke toast subtypes			
LAAS	6 (33.3)	5 (45.4)	
Lacunar	12 (66.6)	6 (54.5)	
CEI	0	0	
Diabetic retinopathy (%)	55 (53.9)	47 (38.2)	< 0.0001
Renal failure (%)	6 (5.8)	7 (5.6)	NS

Modified from Pinto *et al*[19]. CAD: Coronary artery disease; TIA: Transient ischemic attack; LAAS: Large artery atherosclerotic stroke; CEI: Cardioembolic.

due to cardiovascular disease in diabetic subjects with foot ulceration compared to those without foot ulceration[16,17].

In a study conducted by Roper *et al*[18], these authors hypothesized that patients with type 2 diabetes mellitus with diabetic foot could have a poorer cardiovascular prophile with a higher prevalence of sublinical cardiovascular damage and of cardiovascular morbidity. Thus authors evaluated differences between subjects with type 2 diabetes mellitus with and without diabetic foot with regard of: (1) cardiovascular risk profile; (2) previous cardiovascular event prevalence; (3) frequency of markers of asymptomatic cardiovascular damage; and (4) new-onset vascular events incidence. They reported a higher prevalence of major cardiovascular risk factor, of asymptomatic markers of CVD, and a higher prevalence and incidence of previous and new-onset cardiovascular events in diabetic patients with foot complications (Tables 1 and 2).

These findings go along with previous reports of higher degree of cardiovascular morbidity and mortality in diabetic patients with amputations[19,20]. The main cause of death in these patients was coronary artery disease (CAD)[19,20].

Another finding of this study was the higher prevalence of major cardiovascular risk factors such as hypercholesterolemia, LDL plasma levels > 130 mg/dL, hypertriglyceridemia, and microalbuminuria/proteinuria in patients with foot complications compared to diabetic patients without foot complications thus strengthening the issue that DFS in diabetic subjects act as a real and important cardiovascular risk marker.

Authors also reported that patients with diabetic foot were more likely to have a cerebrovascular event [transient ischemic attack (TIA) and ischemic stroke] both on retrospective evaluation (previous TIA and ischemic stroke) and on prospective evaluation (new onset TIA and stroke on a 5 years follow up). The most prevalent subtypes of stroke were lacunar and LAAS subtype (Tables 3 and 4). The higher frequency of lacunar subtype could underline the possible pathogenetic importance of cerebrovascular disease either atherosclerotic and microvessel disease in patients with diabetic foot.

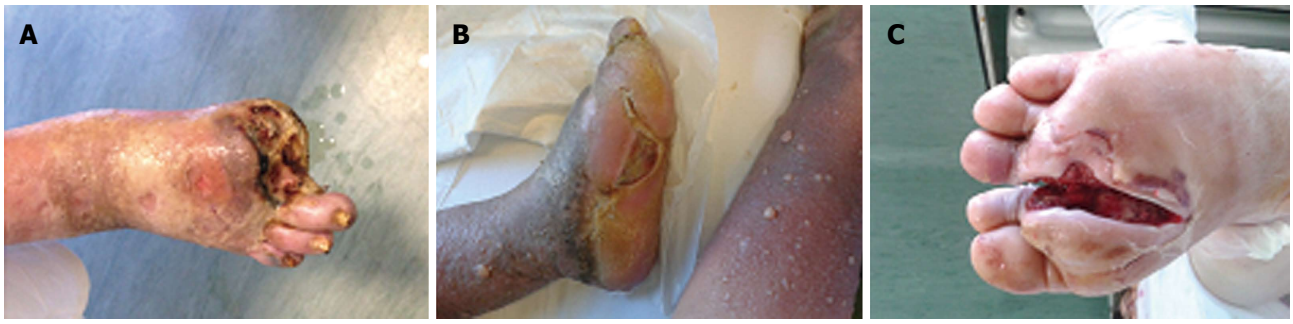

Figure 2 Diabetic foot ulcer. A: Neuroischemic diabetic foot ulcer; B: Neuropathic diabetic foot ulcer; C: Neuroischemic diabetic foot ulcer. Tuttolomondo *et al*[21], personal data.

Table 2 Cox regression analysis of demographic and clinical variables associated with cardiovascular morbidity *n* (%)

	Pts with diabeticfoot (*n* = 102)	Pts without diabetic foot (*n* = 123)	*P*
CAD	12 (11.7)	7 (5.6)	< 0.005
Angina	4 (3.9)	3 (2.4)	< 0.005
Myocardialinfarction	8 (7.8)	4 (3.5)	< 0.001
TIA	6 (5.8)	4 (3.2)	< 0.0001
Stroke	7 (6.8)	5 (4.0)	< 0.005
Renal failure	4 (3.9)	5 (4)	NS
Deaths	14 (13.7)	10 (8.1)	< 0.005
Cardiovascular cause	13 (12.7)	9 (7.3)	
AMI	(3.9)	1 (0.81)	NS
Stroke	3 (2.9)	2 (1.6)	
CHF	3 (2.9)	3 (2.4)	
Other vascular cause	3 (2.9)	3 (2.4)	
Other cause	1 (0.9)	1 (0.81)	

From Pinto *et al*[19]. CAD: Coronary artery disease; TIA: Transient ischemic attack; AMI: Acute myocardial infarction; CHF: Congestive heart failure.

Furthermore cardiovascular risk profile linked to diabetic foot seems to be related to the effects of each cardiovascular risk factor added up a neuropathy and vasculopathy clinical background[21,22], but another further explanation could be in the role of microangiopathy as a pathogenetic background of overall vascular risk.

Another study has been conducted by Pinto *et al*[20] to analyze diabetic foot as a stroke risk marker in type 2 diabetic patients. Authors enrolled 102 type 2 diabetes patients with diabetic foot and 123 diabetic patients without diabetic foot. These authors reported a higher prevalence of previous cerebrovascular events and a higher incidence of new-onset strokes in patients with diabetic foot. They also reported a higher frequency of lacunar and large artery atherosclerosis subtype thus confirming previous findings by the same group of a worse stroke risk profile in diabetic patients with diabetic foot than in diabetic subjects without foot ulceration.

ROLE OF CARDIOVASCULAR RISK FACTORS

Microalbuminuria

Microalbuminuria is defined by the detection of urinary albumin excretion rates of 30 to 300 mg in a 24-h urine collection. It is still the only anomaly of early diabetic kidney that has prognostic value statements. In fact, the appearance of microalbuminuria in diabetic patients is a very important index for progression to overt proteinuria and overt nephropathy. It has been reported as a cardiovascular risk indicator in diabetic populations owing to the fact that microalbuminuria is linked to an increased risk for all-cause and cardiovascular mortality also PAD. In a recent study conducted by Tuttolomondo *et al*[21] authors reported a higher prevalence of microalbuminuria in patients with diabetic foot. These authors also reported a significant positive correlation between microalbuminuria, and interleukin (IL)-6 and resistin serum levels (Tables 5-7).

Table 3 Previous cerebro-vascular events in patients with and without diabetic foot

	Diabetic foot (*n* = 102)	No diabetic foot (*n* = 123)	*P*
TIA	15 (14.7)	9 (7.3)	< 0.0001
Ischemic stroke	18 (17.6)	11.8 (8.9)	< 0.0001
Stroke toast subtype:			
LAAS	6 (33.3)	5 (45.4)	< 0005
LAC	12 (66.6)	6 (54.5)	< 0.005
CEI	0	0	

From Pinto *et al*[20]. TIA: Transient ischemic attack; LAAS: Large artery atherosclerotic stroke; LAC: Lacunar stroke; CEI: Cardioembolic.

Table 4 Incidence of stroke at follow-up in subjects with and without diabetic foot

	Diabetic foot (*n* = 102)	No diabetic foot (*n* = 123)	*P*
TIA	6 (5.8)	4 (3.2)	< 0.0001
Ischemicstroke	7 (6.8)	5 (4.0)	< 0.005
LAAS	4	3	< 0.005
LAC	3	2	< 0.005
CEI	0	0	NS

From Pinto *et al*[20]. TIA: Transient ischemic attack; LAAS: Large artery atherosclerotic stroke; LAC: Lacunar stroke; CEI: Cardioembolic.

HYPERTENSION

Diabetes mellitus and hypertension are frequent comorbidity and they represent two important independent risk factors for atherosclerosis and its complications. Diabetic

Table 5 General and demographic variables in cases and controls *n* (%)

	Pts with diabeticfoot	Pts without diabetic foot	*P*
n	34	37	0.75
Age	66.7 ± 8.5	66.9 ± 7.9	0.027
Sex male	16 (47.1)	15 (41.7)	0.41
Diabetes duration			
< 10 yr	7 (20.6)	21 (58.3)	0.027
= 10 yr	8 (23.5)	11 (30.6)	0.045
= 20 yr	19 (55.9)	4 (11.1)	< 0.001
Treatment			
Diet	4 (11.8)	3 (8.3)	0.65
Oral antidiabetics	3 (8.8)	10 (27.8)	< 0.001
Mixed	6 (17.5)	13 (36,1)	< 0.001
Insulin	21 (61.8)	10 (27.8)	< 0.001
Smoking	7 (20.6)	9 (25)	0.71
Hypertension	20 (58.8)	25 (69.4)	0.041
Dyslipidaemia	14 (41.2)	16 (44.4)	0.35
Obesity	19 (55.9)	13 (36.1)	0.021
Chronic renal failure	15 (44.1)	13 (36.1)	0.064
Mycroalbuminuria	22 (64.7)	6 (14.7)	< 0.001
Retinopathty	19 (55.9)	36 (100)	< 0.001
PAD	10 (29.41)	9 (25)	0.54
CAD	17 (50)	7 (19.4)	< 0.001
TIA/ Stroke	14 (41.17)	6 (16.66)	0.021
Other district atherosclerosis	28 (82.35	21 (58.33)	< 0.001
Artropathy	11 (32.4%)	2 (5.6%)	< 0.001
Neuropathy	25 (73.52)	14 (38.88%)	< 0.001
Diabeticfootgrade			
Grade 0	1 (2.9%)		
Grade 1	6 (17.6%)		
Grade 2	8 (23.5%)		
Grade 3	10 (29.4%)		
Grade4	4 (11.8%)		
Grade 5	1 (2.9%)		
Grade 6	4 (11.8%)		

Data are expressed as median and interquartile (lower and upper quartile). Modified from Tuttolomondo *et al*[21]. PAD: Peripheral artery disease; CAD: Coronary artery disease.

nephropathy has been reported as the main factor that contributes to the development of hypertension in patients with type 1 diabetes mellitus, whereas in patients with type 2 diabetes mellitus, hypertension is an expression of insulin resistance and a clinical finding of metabolic syndrome. Nevertheless, in both type 1 and type 2 diabetes, hypertension heavily influences prognosis and increase the risk of macrovascular and microvascular complications.

Hypertension increases the incidence rate of diabetic retinopathy, nephropathy, and peripheral vascular disease. A study by Pinto *et al*[20] showed a similar prevalence of hypertension in both in patients with diabetic foot and those without it. In addition these authors showed a significant positive correlation between some clinical and laboratory variables such as serum levels of IL-6 and resistin, adipocytokines involved in insulin resistance in the pathogenesis of vascular inflammatory responses (Tables 5-7).

DYSLIPIDEMIA

There are numerous cardiovascular diseases that occur in patients with diabetes, both type 1 or 2. Dyslipidemia in diabetics is strictly linked to cardiovascular disease pathogenesis. The defects in the synthesis and clereance of plasma lipoproteins are among the most commonly metabolic abnormalities that accompany diabetes. The diabetic dyslipidemia, a characteristic pattern characterized by the presence of low levels of high density lipoprotein (HDL) cholesterol, hyper-tigliceridemia, and postprandial lipemia and that is observed more frequently in type 2 diabetes, is one of several factors that contribute to accelerating macrovascular disease in diabetic patients. Among the different factors involved in developing of diabetic dyslipidemia the following should be considered: insulin influences on apoprotein synthesis, regulation of lipoprotein lipase, effect of cholesteryl ester transfer protein, and adipose and muscle and peripheral insulin effects. The acknowledgment and treatment of dyslipidemia are therefore two important elements in the framework of a multidisciplinary approach aimed at the prevention of CAD. However, considering the complexity of the profiles of dyslipidemia in diabetic patients, multiple drugs are often required to achieve therapeutic targets. In addition, the other risk factors usually associated with diabetes mellitus, such as hypertension, hyperglycemia and obesity, should be effectively managed, to reinforce the effects of lipid-lowering therapy. Tuttolomondo *et al*[21] in a recent study reported a high frequency of dyslipidemia in patients with diabetic foot ulcers than in those without diabetic foot also reporting a correlation between dyslipidemia and serum levels of IL-6 and resistin indicating a possible role of inflammation pathogenetic markers on insulin resistance and its linked vascular damage (Tables 5-7).

INFLAMMATION MARKERS IN PATIENTS WITH DFS

In diabetes, there is a complex interplay of several inflammatory and metabolic aspects thus affecting cardiovascular system. Inflammation enhances insulin resistance, that is strictly linked to obesity, diabetes, hyper-tension, prothrombotic conditions and blood lipid disorders[23]. Some studies[22,24-26] suggested a possible interplay between some hormones, inflammatory cytokines and adipose markers such as resistin. Moreover, circulating levels of adiponectin, an important adipocytokine, have been reported as reduced in obesity, type 2 diabetes and CAD[27-29]. This finding could explain how low serum level of adiponectin were linked to low HDL-cholesterol (HDL-C) concentrations[30], low LDL particle size[28], and high serum levels of markers of inflammation[31]. Jeffcoate *et al*[32], reported that it's possible to delineate a inflammatory cascade in diabetic foot pathogenesis as expressed by high serum levels of some inflammatory cytokines such as TNF-α and IL-1β.

Although subclinical inflammation may represent a possible risk determinant of type 2 diabetes and of its vascular complications, available data on diabetic neuropathies are poor. Thus some authors[33] analyzed the possible role of serum levels of some acute-phase

Table 6 Laboratory variables in cases and controls

	Diabetic foot patients	Diabetics without foot complications	*P*
HbA1c	8 (7.28-9.40)	6.85 (6.10-8.00)	0.018
CRP	4 (2.25-5.15)	2.25 (1.90-3.08)	0.041
Total cholesterol (mg/dL)	215.50 (166.50-243.00)	204.00 (185.50-210.00)	0.054
LDL cholesterol (mg/dL)	121.70 (98.75-148.75)	104.50 (78.00-123.00)	0.032
Tryglicerids (mg/dL)	160.50 (119.50-209.25)	180.50 (144.50-199.00)	0.012
Globuli bianchi	12.675 (10775.00-14140.00)	10.700 (8850.00-12027.50)	0.032
Adiponectin (μg/mL)	7.1450 (4.47-12.17)	8.480 (5.15-12.87)	0.022
Resistin (ng/mL)	5.160 (2.96-6.29)	3.290 (2.37-6.5)	0.021
IL-6 (pg/mL)	3.21 (1.23-5.34)	2.13 (1.24-3.97)	0.033

Demographic and anamnestic data are expressed as n° (percentage). Modified from Tuttolomondo *et al*[21]. HbA1c: Hemoglobin A1c; CRP: C-reactive protein; IL-6: Interleukin-6.

Table 7 Correlations of interleukin-1β, adiponectinresistin with clinical and laboratory variables in subjects with diabetic foot

Variable	Adipenectin		Resistin		IL-6
	R	*P* values	*R*	*P* values	
Diabetes duration	0.36 (s)	< 0.001 (s)	0.09	0.37	
Smoking	0.35 (s)	< 0.001 (s)	0.1	0.22	
Hypertension	0.27 (s)	< 0.05 (s)	0.12	0.35	
Dyslipidaemia	0.42 (s)	< 0.001 (s)	0.14	0.15	
Obesity	0.13	0.42	0.12	0.22	
Chronicrenalfailure	0.11	0.56	0.12	0.35	
Mycroalbuminuria	0.08	0.37	0.08	0.37	
Retinopathty	0.1	0. 7	0.1	0. 7	
AOPC	0.11	0.81	0.1	0.77	
CHD	0.46	< 0.001 (s)	0.38 (s)	< 0.0001 (s)	
TIA/stroke	0.12	0.42	0.13	0.32	
Other district atherosclerosis	0.15 (s)	0.42 (s)	0.14 (s)	0.36 (s)	

Coefficients (*R*) and *P* values are calculated by the Pearson correlation mode. Modified from Tuttolomondo *et al*[21]. s: Significative. CRP: C-reactive protein; TNF-α: Tumor necrosis factor-α; IL-1β: Interleukin-1β; IL-6: Interleukin-6; IL-10: Interleukin-10; ICAM-1: Intercellular adhesion molecule-1; V-CAM-1: Vascular cell adhesion molecule-1; vWF: Von willebrand factor; TPA: Tissue plasminogen activator; PAI-1: Plasminogen activator inhibitor-1.

proteins, cytokines, and chemokines. These authors evaluated 10 markers of subclinical inflammation in more than 220 subjects with type 2 diabetic patients and diabetic neuropathy diagnosed by means the Michigan Neuropathy Screening Instrument (MNSI), showing that high levels of C-reactive protein (CRP) and IL-6 were most likely to be linked with diabetic polyneuropathy, high MNSI score, and specific neuropathic deficits, whereas an inverse relationship has been reported with regard of IL-18. This study clearly reported that subclinical inflammation is associated with peripheral nervous system involvement in diabetics.

Nevertheless, few data exist regarding the importance of inflammation markers in patients with DFS. It has well demonstred how low-grade immune activation may represent an risk factor of type 2 diabetes and for its vascular complications such as macrovascular (myocardial infarction and stroke) and microvascular ones (neuropathy and nephropathy).

An immune activation has been reported as important at several stages in the development of chronic wounds. Immune-inflammatory up regulation may precede the incidence of a diabetic foot ulcer in the same way that it precedes some major cardiovascular diabetic complication such as CAD. Owing to the fact that pro- and anti-inflammatory abnormalities could be important in different phase of wound healing, it is suggestive that an immune-inflammatory impairment may damage tissue homeostasis and wound healing leading to the chronic wounds and realizing a complex clinical condition such as DFS.

Weigelt *et al*[34] analyzed the possible relationship between foot ulcers and immune status in diabetic subjects with and without foot ulcers by evaluating some immune mediators. Authors reported how circulating levels of some inflammatory markers such as acute-phase proteins, cytokines, and chemokines were higher in patients with diabetic foot. Authors showed an higher degree of serum levels of CRP, fibrinogen, IL-6, macrophage migration inhibitory factor, macrophage inflammatory protein-1β, and interferon-γ-inducible protein-10.

However, since the existence of a strict relationship between inflammatory and adypocite dysfunction marker, a possible interesting issue should be to evaluate the role of adiponectin, resistin and inflammatory cytokines in patients with diabetic foot compared with those without foot complications.

A recent study by Tuttolomondo *et al*[21] has been conducted with this aim and and authors analyzed serum levels of adiponectin, resistin and IL-6 in subjects with diabetic foot in 34 patients with type 2 diabetes mellitus and foot ulceration and in control subjects with type 2 diabetes mellitus without foot ulceration (Table 5). This study reported how diabetics with diabetic foot showed compared to diabetics without diabetic foot showed higher IL-6 and resistin plasma levels and lower adiponectin plasma levels (Table 6). Resistin, strictly involved in pathogenesis of insulin resistance, may also have inflammatory interactions. A study[35] reported that lipopolysaccharide increased resistin expression in rat WAT, 3T3-L1 adipocytes and human monocytes. Studies conducted in animal models (murine) showed not univocal findings with regard a possible role of pro-inflammatory cytokines as regulation factors of resistin, nevertheless recent human studies reported and underlined a role

of inflammatory cytokine on resistin induction[36,37]. Osawa *et al*[38] reported how high serum resistin levels play as independent risk factor for ischemic stroke in a Japanese population also showing that high resistin serum levels associated with diabetes or hypertension furtherly increased cerebrovascular risk. Findings by Tuttolomondo *et al*[21] with regard of higher plasma levels IL-6 plasma levels and resistin in diabetic subjects with foot ulceration in comparison with diabetics without foot complications seem to confirm this issue.

Reilly *et al*[39] reported the role of resistin as a metabolic mediator of an interplay between inflammation and atherosclerosis. In contrast with resistin, adiponectin may inhibit resistin-mediated increase in vascular cell adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule 1 (ICAM-1) serum levels[40,41].

Thus hypo-adiponectinemia can represent an early indicator of a complex cardiovascular risk factor pattern predisposing to atherosclerosis and its organ-end damage complications as well as a contributing factor increasing progression of the atherosclerotic plaque.

Adiponectin has anti-inflammatory and athero-protective actions in various tissues by an inhibition action of the expression of vascular adhesion molecules and scavenger receptors, a reduction of expression of the inflammatory cytokine TNF-α, increasing of NO production and lowering the proliferation and migration of smooth muscle cells[42]. To date, two receptors mediate adiponectin's actions in lipid and glucose metabolism such as ADIPOR1 and ADIPOR2[43]. Halvatsiotis *et al*[44] reported how a sequence variant in the intron 5 of the ADIPOR2, rs767870 is more significantly associated with cardiovascular disease in a Greek population.

Findings by Tuttolomondo *et al*[23] of lower median plasma levels of adiponectin in subjects with diabetic foot seem to confirm this issue. Furthermore the same authors reported a significant negative correlation of adiponectin plasma levels with cardiovascular risk factors such as hypertension, dyslipidaemia and with previous cardiovascular events such as morbidity such as previous TIA/Stroke and new onset events such as neuropathy, micro- albuminuria thus further underlining the role of hypo-adiponectinaemia as a predictive factor of cardiovascular events.

Adipose tissue has also inflammatory properties as expressed by cytokine production[45], thus it's possible to hypothesize the existence of an "adipo-vascular" axis[46], strictly involved in the pathogenesis of increased cardiovascular risk in patients with type 2 diabetes. Findings such as lower degree of serum adiponectin levels and and higher degree of IL-6 serum levels may represent the pathogenetic and biological phenotype of this "adipo-vascular axis" in subjects with DFS involving both microvascular and inflammatory mechanisms.

Some authors[47] analyzed adipocyte volume and its association with tumor necrosis factor alpha (TNF-α), IL-6, adiponectin and high sensitivity CRP (hs-CRP) levels showing how mean adipocyte volumes were higher in obese diabetic patients than in other groups. Authors also reported a significant positive correlation between adipocyte size and inflammatory markers, whereas a negative correlation has been reported between adipocyte size and adiponectin levels. These findings furtherly confirm the existence of an adipose-inflammatory vascular axis strictly involved in diabetic complications such as DFS owing to the fact that adiposity and its related conditions, such as diabetes, are at the same time pro-inflammatory and inflamed conditions.

The evaluation of association of adipokines with the macrovascular complications of type 1 diabetes mellitus (DM) was the aim of a study[48] that analyzed serum adiponectin, leptin, and resistin levels in type 1 DM patients evaluating their association with carotid intima media thickness (CIMT). Authors showed how adiponectin is negatively correlated with CIMT, age, BMI, waist-to-hip ratio, and that exist a correlation between resistin and CIMT and systolic blood pressure.

Indeed recent studies suggest that adiponectin may influence inflammatory vascular interactions by means a down-regulation of adhesion molecules expression on endothelial cells[47], inhibition of endothelial cell NF-kB signaling[48], and lowering macrophage function[49,50]. Other studies showed how adiponectin can inhibit TNF-α mediated expression of E-selectin, VCAM-1 and ICAM-1 in human endothelial cells[47-49,51,52]. These findings furtherly confirm the vasoprotective action of adiponectin45[53-60] and how this molecule may negatively modulate atherogenesis also by means its influence on inflammatory variables such as TNF-α.

The pathophysiology of insulin resistance and atherosclerosis share a common inflammatory basis. Thus some authors[59] to test this hypothesis, evaluated 40 patients with a myocardial infarction [M]. Endothelium-dependent flow-mediated dilation (FMD) and -independent nitroglycerine vasodilatation (determined by ultrasound), S(I) (insulin sensitivity index; determined by isoglycaemic-hyperinsulinaemic clamp) and serum levels of CRP, TNF-α, IL-6, resistin and adiponectin (determined by ELISA) were measured. FMD, S(I) and adiponectin levels resulted significantly lower in patients with T2DM, whereas TNF-α and IL-6 levels have been observed as significantly higher in patients with T2DM. Authors also reported that TNF-α concentrations and brachial artery diameter were negatively, whereas S(I) was positively, correlated with FMD. These results indicate how endothelium is negatively impacted in multiple ways by the diabetic state after an MI also suggesting endothelium as the main organ-target of adipose-inflammatory dysfunction of diabetes.

Furthermore, in a recent paper Zietz *et al*[49] reported an association between low levels of adiponectin and low levels of HDL-cholesterol and how this relationship seems to act as independent cardiovascular risk factor. The same authors also reported that high levels of adiponectin are associated with high levels of HDL-cholesterol thus suggesting how adyponectin can be involved in a so called "cardioprotective" pathway together with HDL levels. This findings could find a confirmation in results reported by Tuttolomondo *et al*[21] showing respectively a positive

Table 8 Diabetic foot infection classification schemes: Infectious Diseases Society of America Infectious Diseases

Clinical description	Infectious Diseases Society of America
Wound without purulence or any manifestations of inflammation	Uninfected
⩾ 2 Manifestations of inflammation (purulence or erythema, pain, tenderness, warmth, or induration); anyc ellulitis or erythemaextends 52 cm around ulcer, and infection is limited to skin or superficial subcutaneous stissues; no localcomplications or systemic illness	Mild
Infection in a patientwho is systemicallywell and metabolicall ystable buthas 2 cm; lymphangitis; spread beneath fascia; deeptissue abscess; gangrene; muscle, tendon, joint, or bone involvement	Moderate
Infection in a patient with systemic toxicity or metabolic instability (*e.g.*, fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, hyperglycemia, or azotemia)	Severe

Adapted from Lavery *et al*[67].

(for IL-6 and resistin) and negative [for adiponectin] correlation in subjects with diabetic foot with regard of some metabolic markers and some clinical and laboratory variables. Recently DFS has been reported by Pinto *et al*[19] as a predictive factor of cardiovascular morbidity in diabetic patients.

Other research underlined the positive correlation between inflammatory cytokines and cardiovascular morbidity in diabetic patients. Tuttle *et al*[52] reported higher degree of serum levels of IL-6 and TNF-α in diabetic women with and without CVD compared to nondiabetic women thus suggesting a common inflammatory state in both diabetes and cardiovascular diseases.

In diabetic foot have been described some abnormalities such as an inflammatory state, low collagen levels due to low synthesis and higher degradation and these changes have an important role in impairment of wound healing. Cathepsin D, an aspartic endopeptidase is able to reverse the inhibition of collagen biosynthesis in wounded rat skin with diabetes. Some authors[54] reported how patients with diabetic foot ulcer have higher median plasma level of Cathepsin D and lower median plasma levels of adiponectin, also showing a positive correlation between variables such as ulcer severity, BMI, A1c and retinopathy and Cathepsin D and a negative correlation with adiponectin. Thus most of research experiences seem to suggest that atherosclerosis in diabetes could be a real inflammatory disorder. A study[60] evaluated the prevalence of inflammatory markers such as high-sensitivity CRP, adiponectin, and nuclear factor-κB (NF-κB) expression, in peripheral blood mononuclear cells in patients with type 2 diabetes mellitus (T2DM) with and without macrovascular disease. Authors reported how diabetic subjects with T2DM showed a higher hsCRP and NF-κB expression and a lower degree of adiponectin serum levels compared to healthy controls.

INFECTIONS IN PATIENTS WITH DFS

Definition of diabetic foot infections (Table 8) indicate infectious diabetic foot as a "clinical syndrome characterized by the presence of local signs of inflammation such as redness, warmth, induration, pain or tenderness and purulence, sometimes in the context of a framework of sepsis, that occurs in a site below the malleoli in a person with diabetes"[61]. Infections on diabetic foot can represent a common and dangerous complication of diabetes owing to the fact that they can involve deeper soft and bone tissuse (cellulitis and osteomyelitis) thus significantly increasing the risk of amputation.

Diabetes is the main cause of non-traumatic amputation of the lower limbs in the world. In a recent study[62,63] enrolling patients with DFS, infections increased the risk of a minor amputation by 50% compared to patients without infection. Among factors able to predispose to infections on diabetic foot it's possible to include: foot ulcer duration of longer than 30 d, a history of recurrent foot ulcers, traumatic causes, peripheral vascular disease and neuropathy.

Wound infections are polymicrobial including gram-positive cocci (Staphylococcus aureus, β-streptococci, usually group B, or coagulase-negative staphylococci), Gram-negative rods (*e.g.*, *Escherichia coli*, Proteus, Klebsiella), sometimes including non-fermentative Gram-negatives (*P. aeruginosa*), and anaerobes (*e.g.*, *Finegoldia, Bacteroides*).

Infectious Disease Society of America (IDSA) guidelines indicate that infection on diabetic foot is present when there is purulent drainage and/or the presence of two or more signs of inflammation[63]. Possible infection signs are: fever, chills, hypotension, anorexia, nausea, vomiting, change in mental status and hyperglycaemic state and blood abnormalities such as leukocytosis, elevated sedimentation rate, CRP or procalcitonin levels or positive blood cultures are further signs of a severe infection. Nevertheless in more than 50% of patients with diabetes and infectious DFS these signs were absent[64].

Different classification systems developed in the last years for the stadiation of diabetic foot infections, but a widely accepted method is the IDSA classification scheme, with four progressive levels of infection and with a good correlation with clinical findings[65,66].

The diabetic foot ulcers require an appropriate antimicrobial treatment preferably targeted on the basis of microbiological culture and that includes agent active against gram positive cocci which are the most common pathogens. Surgical management is sometimes necessary.

PERIPHERAL ARTERIAL DISEASE AND DFS

Diabetic foot ulceration (DFU) with its high morbidity and mortality represents an important cause of hospitalization in

diabetics and it is an independent risk factor for peripheral arterial disease. PAD, presents in half of patients with DFU, is a condition characterized by steno-obstructive lesions downstream of the renal arteries that lead to a reduction in the perfusion of the lower limbs and it represents a common cause of impaired ambulation and is a leading cause of lower extremity wounds and amputations[53,54]. In fact, diabetes mellitus which can be considered as a whole as an inflammatory disease is burdened with microvascular complications such as nephropathy, retinopathy and neuropathy and macrovascular complications including stroke, myocardial infarction (MI), and PAD that occur earlier than in nondiabetic patients and the underlying pathologies are often more diffuse and severe.

Microvascular and macrovascular complications of diabetes although they affect small vessels, and large vessels, have a similar pathogenetic background. Chronic hyperglycemia has a leading role in this pathogenetic pathway that leads to vascular complications by means either metabolic and structural abnormalities such as advanced glycation end products (AGE) production, activation of protein kinase C (PKC), high degree of reactive oxygen species (ROS, oxygen-), and impairment hemodynamic regulation and activation of the renin-angiotensin system (RAS).

Other pathogenetic factors are inflammation, coagulation disorders, smooth muscle cell involvement, endothelial dysfunction, impairment of blood supply and impairment of platelet action.

Diabetic arteriopathy is characterized by changes in the arterial wall that include arterial narrowing with increased intima-media thickness. The first site of injury is the vascular endothelium that is the central candidate barrier against atherogenesis process. Endothelium produces important substances such as nitric oxide (NO) that induces vasodilatation and also regulates platelet-vessel wall interaction, thereby functioning as an antiplatelet agent.

The alterations that occur in diabetes such as chronic hyperglycemia and insulin resistance alter the endothelial production of NO and impaired arterial vasodilation in diabetes. In addition to the reduction in the vasodilatory response in diabetes occurs overproduction of vasoconstrictor substances such as endothelin 1. This endothelial dysregulation causes structural and functional alterations that characterize the later diabetic arterial disease[67-69]. Another atherosclerotic pathogenetic background is an inflammatory activation. In fact, an increased expression of adhesion molecules induces inflammatory cells cross endothelial barrier and reach into intima media of the vessel wall and subsequent ingesting oxidized LDL and forming foam cells, an important component of atherosclerotic fatty streaks that represent an early marker of macrovascular disease.

Impairment in coagulation, fibrinolysis, and platelet action, represents the basis of the thrombophilic state leading to increased risks for thrombogenesis, atherosclerosis progression, and plaque events which are involved in the development of cardiovascular complications in diabetes. Age and duration of diabetes are strictly related with frequency of PAD in both diabetic and nondiabetic patients. Other risk factors such as hypertension, smoking, and blood lipid disorders have a high prevalence in diabetic subjects thus enhancing vascular risk. However, if the supply of blood fails to satisfy ongoing metabolic requirements as a consequence of arterial narrowing, symptoms will occur, the severity of which depends on the degree of arterial narrowing, number of arteries affected, and the activity level of the patients. PAD can present with pain of one or more lower extremity muscle groups related to activity (intermittent claudication), atypical pain, pain at rest, or with nonhealing wounds, ulceration, or gangrene.

Clinical history and physical examination are essential to diagnose a condition of PAD in a diabetic subject. Suggestive of PAD diagnosis are a history of intermittent claudication, coronary artery disease, cerebrovascular events, foot ulcers, angioplasty, or surgical bypass.

Objective exam can help to determine the extent and distribution of peripheral vascular disease[70,71] in diabetics, but measurement of the ankle-brachial index (ABI) calculated as systolic blood pressure at posterior tibial or dorsalis pedal level compared with brachial blood pressure, is a useful method to evaluated an occlusive PAD. An ABI of $\leqslant$ 0.90, is higly sensitive and specifical for a diagnosis of PAD. To assess the severity of the perfusion, the evaluation of below-knee vessels is particularly important in patients with diabetes and duplex ultrasound is a first line investigation[72].

Multiple factors impair wound healing in diabetes in addition to PAD. Patients with mild PAD and ABI > 0.6, should be initially managed with local wound care (debridement and treatment of infection) and a period of observation. Extended ulcers and infected ulcers with a poor extended outcome a early vascular intervention may be required[73]. Revascularization is indicated for critical limb ischemia and for some patients with claudication. Surgical risks and the degree of severity of foot ulcers may influence the surgical therapeutic option *vs* endovascular intervention. Thus depending upon the characterization of a given arterial lesion, a diabetic patient with PAD may benefit from a surgery-first or an angioplasty-first approach. Most diabetics with critical ischemia have popliteal/tibial site of occlusion thus therapeutic option requires a surgical approach below-the-knee or bypass grafting[74].

A study conducted by Ciccone *et al*[75] evaluated the outcome of patients with diabetic foot who underwent angioplasty (PTA) revascularization. Authors reported at 1 year follow-up, a "major"/"minor" events incidence of 15%. Authors also reported that obesity, high LDL levels and an arterial lesion at a distal site were statistically significantly associated with major events and how high levels of inflammatory markers such as PCR had a significant relationship with the ulcer recurrence.

The results of this study highlighted the fact that diabetic foot disease is an important social problem because of the hight incidence in the population and the risk of major and minor complications and therefore a rapid diagnosis and prompt revascularization treatment, if needed, are essential to improve the quality of live

and prolong survival. Nevertheless, other experimental therapeutic options could be useful in clinical setting of diabetic foot ulcerations. Clinical care of patients with foot ulcers and infection is not easy and often it is required a revascularization treatment by surgical or endovascular approach. However, it is appropriate to consider novel therapeutic approaches such as extracorporeal shockwave (SW). Extracorporeal SW therapy could improve the natural course of such a disease due to its action on the endothelium of blood vessels to improve angiogenesis and ameliorate symptoms in patients with limb ischemia. A recent study conducted by Ciccone *et al*[76] analyzed the effects of SW therapy in patients with PAD. In this study twenty-two patients were enrolled and were randomly assigned into two groups: SW treatment (12 patients, 67 ± 9 years) and control (10 patients, 68 ± 12 years). Stenosis greater than 75% causing a hemodynamic impairment was treated with SW therapy. All patients underwent a Doppler ultrasound of the lower limb arteries in their entirety and a clinical-functional evaluation of their condition (*e.g.*, ABI) before and after the treatment. Findings of this study showed a significant improvement of stenosis degree after treatment in patients treated with SW.

In addition, a significantly higher number of treated patients than controls showed a reduction in the Fontaine stage. On the basis of these data, although studies in larger samples are needed to confirm the results of this study, the authors hypothesized that SW therapy could represent a useful tool in PAD therapy, and may prepare patients for more aggressive therapy.

FOCUS ON NON ALCHOLIC FATTY LIVER DISEASE AND DIABETES

Non-alcoholic fatty liver disease (NAFLD) is a frequent comorbidity in diabetic subjects (type 2 diabetes mellitus) and in those with metabolic syndrome (MS), with a frequence of more than 30%. NAFLD represents the hepatic organ damage related to MS that encompasses multiple cardiovascular risk factors and that recognize as central pathogenetic basis insulin resistance and as clinical expression several diseases such as visceral obesity, hypertension, blood lipid disorders and type 2 diabetes. The term NAFLD encompasses some hepatic disorders with the primary pathologic findings of microvesicular hepatic steatosis that occurs without a clinical history of significant alcohol consumption. In this clinical setting context it has been distinguished a disease with histologic essential fat accumulation (steatosis) and a disease in which steatosis coexists with a state of liver-cell injury and inflammation called non-alcoholic steatohepatitis (NASH). These two conditions show an increased prevalence and incidence thus becoming a real public health problem due to their strict relationship with diabetes and obesity pandemias. The pathogenesis of NAFLD is not fully clear, but insulin resistance appears to be as the main pathogenetic metabolic event, even if many other predisposing conditions such as obesity, oxidative stress, cytokine/adipokine axis have been reported as plausible coexisting pathogenetic[77].

Insulin resistance represents the clinical expression of the inability of endogenous insulin to enhance glucose uptake and its utilization and it is the physiopathological main factor able to induce the metabolic syndrome. Insulin acts by means of binding to its plasma membrane receptor and its effects are mediated by a series of cellular messengers acting by mechanisms of protein-protein interactions that have been reported as impaired by several factors such as increased levels of fatty free acids (FFAs), oxidative damage, inflammation and abnormalities of cytokines/adipokines interplay able to induce a peripheral (muscle and adipose tissue) and hepatic insulin resistance. Insulin resistance enhances hepatic lipid accumulation thus increasing liver FFA influx and stimulating some enzymes involved in lipogenesis in liver and thus may be indicated as the typical physiopathological finding of NAFLD[78]. Furthermore, visceral fat plays a central role in the pathogenesis of insulin resistance and NAFLD owing to the fact that adipose tissue is not an inert tissue but it acts as a real active endocrine organ, thus furtherly impairing insulin resistance and influencing cytokine/adipokine pathways in terms of increased levels of FFA, adiponectin, leptin, TNF-α, IL-6. In particular adiponectin acts as a leading mediator in this pathogenetic events and its decreased levels are directly related to steatosis grade owing to the fact that adiponectin has a protective role decreasing lipid accumulation and fibrosis processes in liver[79].

Fatty free acids represent a well demonstred pathogenetic markers of insulin resistance and of its complications such as NAFLD owing to the fact that FFA cause liver cellular apoptosis and impair interplay between hepatic cells and immune system, cytokines, ROS and finally also impairing insulin production and signaling mechanisms[80-86].

FFA and their derivatives induce insulin resistance, increase liver inflammation and promote instability in atherosclerotic plaque by a common pathogenetic pathway involving Jun N-terminal kinases (JNKs) that are one of the mitogen-activated protein kinase (MAPK) superfamily as pointed out by some authors in a recent work[87]. High degree of oxidative stress and its related JNK activation, as well as an impaired activation of pro- and anti-apoptotic proteins of the Bcl-2 family has been reported as factors able to contribute to hepatocyte apoptosis in a murine model of non-alcoholic steatohepatitis[88]. Therefore, a direct role is attributed to FFAs that seem able to directly cause the apoptotic events by activating the proapoptotic protein Bax, by menas c-jun N-terminal kinase-dependent mechanisms as reported by a recent study conducted by Tarantino *et al*[89]. In this study authors analyzed the relationship between anti-apoptotic serum Bcl-2 concentrations and grade of steatosis and inflammation in subjects with NAFLD and steatohepatitis (NASH) reporting a significant predictive value of Bcl-2 serum levels towards a higher frequency of metabolically unhealthy overweight/obese patients (MUOs) (obese subjects without hepatic steatosis) suggesting that the anti-apoptotic process could have a significant role to block FFA hepatotoxic actions. Although the development of NAFLD has some common mechanisms with the

development of metabolic syndrome, as they share the pathophysiologic basis of insulin resistance, NAFLD is currently not a component of the diagnostic criteria for metabolic syndrome. Nevertheless a recent study showed that ultrasonographically detected NAFLD could act as a possible predictive factor of insulin resistance[90,91]. On this basis US-NAFLD could be used as a new criterion to define metabolic syndrome also in consideration of the high sensitivity and specificity of abdominal US in the diagnosis of NAFLD. These data have been underlined by Tarantino *et al*[91] in a recent article. In the light of the various pathways thought to be central in the pathogenesis of NAFLD, the main therapeutic approach consists in the modification of risk factors, in particular lifestyle through diet and physical activity and the more promising pharmacological approach seems to be the use of drugs able to improve insulin sensitivity such as metformin and PPAR (Peroxisome Proliferator Activated nuclear Receptor agonist). However, further studies on the pathogenesis of NAFLD would be needed to identify new potential therapeutic targets in these patients and to define the most appropriate pharmacological and non-pharmacological therapeutic approach. Therefore, NAFLD is commonly associated with the metabolic syndrome which is considered as the hepatic expression and results from a complex interaction between genetic and environmental factors with insulin resistance as a fundamental pathogenic mechanism and in consideration of the progressive increase in the prevalence of insulin resistance, NAFLD/NASH should be considered as emerging diseases, involving a high percentage of the Western population.

CONCLUSION

Diabetic foot and its related clinical conditions such as foot ulcers and infective complications represent the most common cause of hospitalization in subjects with diabetes. Management of DFS and its related treatment of infectious diabetic foot and amputations also represent a health problem in terms of cost (several millions of euro every year).

"The majority of foot ulcers appear to result from minor trauma in the presence of sensory neuropathy." This sentence[92] underlines the critical pathogenetic triad of DFS in diabetics: peripheral sensory neuropathy, deformity, and trauma. These risk factors have been reported as present in more than 60% of diabetic foot complications.

Our review aimed to underline the complex metabolic and inflammatory interplay that could explain high cardiovascular event rate of patients with diabetic foot. Diabetic vascular complications recognize a well described inflammatory pathogenesis, but only few studies evaluated immune-inflammatory background of DFS.

Only a few previous studies[18-21] evaluated inflammatory markers such as cytokine and adypokines in patients with diabetic foot. Nevertheless several reports clearly underlined the role of low serum level of adiponectin that has been reported as complex metabolic and inflammatory axis able to predispose to atherogenesis. Adiponectin with its anti-inflammatory and vascular effects in is able to inhibit inflammatory effects of vascular adhesion molecules and scavenger receptors and to lower the expression of the inflammatory cytokine TNF-α, furthermore adiponectin enhances NO production and inhibit the proliferation and migration of smooth muscle cells[93].

Findings reported by Tuttolomondo *et al*[21] of low serum levels of adiponectin and the significant negative correlation between adiponectin and several traditional cardiovascular risk factors in subjects with diabetic foot could represent a well confirmation of this issue. Thus owing to the fact that several cytokines are also produced by adipose tissue[46] it has been hypothesized that the high rate of cardiovascular events in diabetes could be due to a pathogenetic axis called as an "adipo-vascular" axis[44]. This "adipo-vascular axis" represented by low serum levels of adiponectin and high serum levels of IL-6 and resistin could be related to foot ulcers pathogenesis by microvascular and inflammatory mechanisms.

Adiponectin has been also reported by recent studies as involved in the regulation of inflammatory vascular response by reducing the expression of adhesion molecules on endothelial cells[62], impairing endothelial cell NF-κB-related mechanisms[45] and altering macrophage actions[64]. A recent research also reported how adiponectin inhibits the TNF-α related expression of E-selectin, VCAM-1and ICAM-1 in human endothelial cells[46] thus indicating how adiponectin has been evaluated as real vasoprotective and anti-atherogenic factor .

Recently, Ouchi *et al*[48] showed how low degree of serum adiponectin is linked to low levels of HDL-cholesterol, thus representing a real independent cardiova-scular risk factor, whereas high levels of adiponectin are associated to a protective cardiovascular risk profile associated to high levels of HDL-cholesterol. Findings by Tuttolomondo *et al*[21] of a positive (for IL-6 and resistin) and negative (for adiponectin) correlation in subjects with diabetic foot between these immuno-inflammatory and metabolic markers and some clinical and laboratory variables could represent a further confirmation of the crucial role of inflammatory and metabolic "milieu" such as cytokines and adipose hormones in foot complications in diabetics, as already reported for other vascular complications of diabetes.

Thus inflammation marker evaluation has in DFS multiple points of potential importance concerning a better evaluation and analysis of these crucial key points: (1) pathogenetic role in ulcers and their micro and macro-vascular background; (2)possible link between inflammation state and adipo-metabolic axis; (3) predictive role towards foot complications such as ulcers incidence; (4) putative role as markers of gravity of wounds and ulcers in a diabetic foot; (5) association with cardiovascular co-morbidity (prevalent and incident) in subjects with DFS; (6) prognostic role towards ulcer healing; (7) strict association with peripheral artery comorbidity (PAD); and (8) pathogentic links with metabolic syndrome and NASH[93-99].

It explains that a strict and prospective inflammation

marker evaluation could be useful in practical management of foot complications in diabetic subjects in every medical setting (Internal Medicine, Diabetology, Surgery, Orthopedics) to better evaluate a complex disease such as DFS in a multispecialistic management contest.

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