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Metabolic and Non-Metabolic Peripheral Neuropathy: Is there a Place for Therapeutic Apheresis?

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ABSTRACT

As the rate of obesity and the incidence of diabetes mellitus have been increasing, diabetic neuropathy has become the most common cause of peripheral neuropathy in developed countries. In addition, a variety of pathogenetically heterogeneous disorders can lead to impairment of the peripheral nervous system including amyloidosis, vitamin deficiencies, uremia and lipid disorders, alcohol abuse, autoimmune and infectious diseases as well as exposure to environmental toxins. We have noted that a combination of these disorders may aggravate the manifestations of peripheral diabetic neuropathy, an effect, which is most pronounced when metabolic and non-metabolic pathologies lead to cumulative damage. Current treatment options are limited and generally have unsatisfactory results in most patients. Therapeutic apheresis (INUSpherese®) allows the removal of metabolic, inflammatory, immunologic and environmental contributors to the disease process and may be an effective treatment option. We reviewed the developments in therapeutic apheresis for metabolic and non-metabolic peripheral neuropathy, including the current literature as well as data from our university diabetes center.

Introduction

There is an increasing prevalence of peripheral neuropathies (PNs) worldwide. These neuropathies differ in etiopathogenesis and have in common structural damage to the peripheral nervous system leading to symptoms such as numbness, and prickling or tingling sensations in the feet or hands frequently spreading upward from the legs to the arms [1–4]. Moreover, patients frequently complain of enhanced sensitivity to touch and/or sharp, jabbing or burning pain. PNs may be acute or chronic and involve just one nerve, described as "mononeuropathy", or, more frequently, affecting multiple nerves, frequently in similar areas of all four peripheral extremities and is referred to as "polyneuropathy" [1–4]. In addition to these symptoms resulting from impairment of sensory nerves, neuropathy can affect autonomic nerve fibers as frequently seen in patients with peripheral neuropathies such as diabetic neuropathy. In these patients, a variety of troublesome and disabling symptoms reduces quality of life including e. g. orthostatic hypotension, gastroparesis, impaired sweating, bladder dysfunction, erectile dysfunction or diarrhea alternating with constipation [5]. These symptoms pose a challenge to the clinician as autonomic testing is technically demanding and symptomatic treatment requires personalized multimodal regimens to be effective [6]. Autonomic involvement is frequently seen in patients with diabetic neuropathy but can also occur as consequence of amyloid deposition, as part of a paraneoplastic syndrome as well as in a variety of inflammatory, toxic, hereditary and metabolic disorders [7].

PNs are usually caused by systematic processes that affect the entire body. By far, the most common cause in our modern society is diabetes mellitus and/or impaired glucose tolerance [8–10]. Formation of toxic advanced glycation end-products (AGEs) have been reported to be involved in a major fashion in the pathogenesis of diabetic neuropathy. The mechanisms, however, of this phenomenon appear to be multifactorial and not fully explored [8–10]. In fact, more than 100 etiologies of PNs have been identified, including various metabolic disorders, vitamin deficiencies, autoimmune and inflammatory diseases, blood disorders, and exposure to exogenous toxins, including alcohol, certain drugs and environmental pollutants [1–4, 8].

In addition to the frequently severe discomfort of the affected patients owing to nerve damage, peripheral polyneuropathy predisposes to many other devastating complications. These include problems with wound healing and ulcers that may lead to systematic sepsis or amputations. They may also lead to gain abnormalities and muscle weakness, both predisposing for bone fractures and long-term morbidity and mortality [8]. Therefore, PNs constitute a major challenge for our health care and economic systems (26 % of the patients with PNs were early retirees with 52 years). Current treatment options involve antidepressants, antiepileptics, opioids, and non-steroidal anti-inflammatory drugs; all are purely symptomatic [1–3, 9, 11]. Other compounds employed include aldose-reductase inhibitors and acetyl-l-carnitine and thioctacid, which, however, have not been superior to placebo [1–3, 9].

Metabolic causes of PNs

The most common cause of PNs is diabetes mellitus (DM). About half a billion people are affected by DM worldwide; half of these will have some degree of PNs making this condition one of the most common disorders in medicine. In patients with DM, patterns and factors associated with PNs include old age, duration of diabetes, presence of obesity, and/or hypertension [12]. Furthermore, albuminuria has been identified as an independent predictor of PNs, as well as glycemic variability [13]. Enhanced serum C-reactive protein (CRP) levels, but not blood monocyte count, and a monocyte count to high-density lipoprotein to cholesterol ratio (MHR), indicating enhanced inflammation and oxidative stress, were independently associated with PNs [14].

A medical disorder such as diabetic PNs is in itself already quite complex, and it becomes even more challenging when the clinical picture is aggravated by other metabolic and non-metabolic pathogenetic factors. Thus, it has been reported that triglycerides, remnant lipoproteins, and other lipids, which are frequently elevated in the course of metabolic syndrome, are contributing to the disease process and constitute independent risk factors [15–17]. Furthermore, high levels of uric acid correlate positively with both the clinical and electrophysiological worsening of diabetic sensorimotor polyneuropathy [18]. Finally, vitamin B deficiencies known to cause PNs are still widely underestimated and not adequately supplemented in patients with diabetic PNs. This is especially important in DM patients who are on chronic metformin treatment, as the state-of-the art first line drug for Type 2 diabetes mellitus has been associated with a high prevalence of vitamin B12 deficiency [19]. Chronic treatment with metformin, especially at high doses, has increased the occurrence of Vitamin B12 deficiency up to 50 % in some patient groups [20, 21].

Vitamin B12 deficiencies affect 2–20 % of DM patients depending on the population studied [20, 21]. Therefore, it has been suggested to provide a Vitamin B12 supplementation to all DM patients receiving metformin [20, 21].

Last, but not least, alcohol toxicity and its complications have been called "a double trouble" when combined with DM [22]. Given that up to 50 % of the Western population consume alcoholic beverages, the combined toxicity of glucose and ethanol has been largely underestimated. In our own clinical cohorts, patients with advanced angio-neuropathic diabetic foot syndrome present with a combined history of diabetes mellitus and excessive alcohol consumption. There is ample evidence that diabetic patients who regularly consume alcohol have an augmented risk of developing severe diabetic PNs [22]. Alcohol-induced peripheral neuropathy is caused by the impairment of neural function and thinning of the myelin sheath covering nerve fibers [22]. Furthermore, alcohol augments cellular oxidative stress, creating free radical damage in the already malfunctioning nerves in PNs.

Other metabolic disorders, which may be related to metabolic syndrome, include chronic kidney or NAFLD and NASH. Finally, metabolic and endocrine diseases, such as hypothyroidism, porphyria, amyloidosis, and Fabry disease have been associated with PNs.

Up to 10 % of PNs may be associated with dysproteinemia with the majority presenting with monoclonal gammopathy of undetermined significance (MGUS).

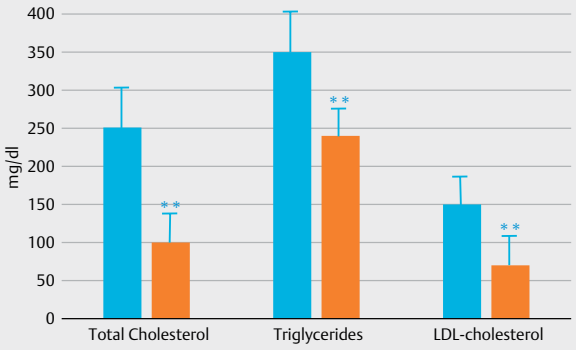
Inflammatory, autoimmune, and toxic causes of PNs

There is a wide spectrum of PNs not primarily caused by metabolic diseases. A complete review of all of these forms of PNs would go beyond the scope of this article. There are several excellent reviews presenting the manifestations and mechanisms of these neuropa-

thies in more detail [1, 3, 23]. Patients with inflammatory and autoimmune conditions related PNs may present with additional sensorimotor symptoms and ataxia [2].

Inflammatory diseases, including infectious and autoimmune disorders, are frequently associated with PNs. This group of diseases involve, among others, the Guillain–Barré syndrome, systemic lupus erythematosus, leprosy, multiple sclerosis, Sjögren syndrome, babesiosis, Lyme disease, vasculitis, and sarcoidosis.

Genetic diseases encompassing PNs include Friedreich ataxia, Fabry disease, Charcot–Marie–Tooth disease, hereditary neuropathy with liability to pressure palsy, as well sodium channel mutations and transthyretin familial amyloidosis with polyneuropathy. For the latter, novel specific RNA interference therapeutic agents which inhibit hepatic synthesis of transthyretin are currently tested in clinical trials [2].

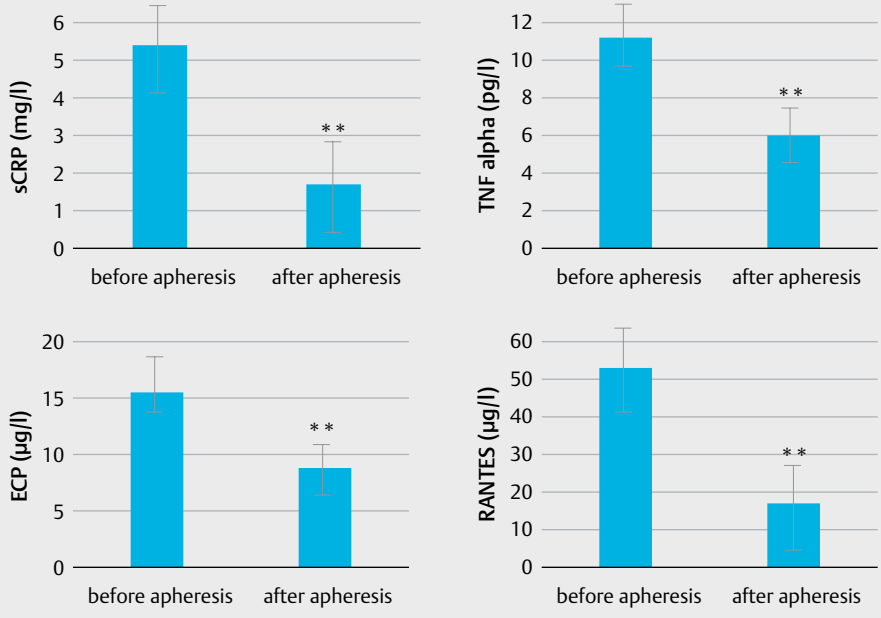


▶ **Fig. 1** Effect of INUSpheresis® on dyslipoproteinemia in patients with polyneuropathy (before and after apheresis). ** indicating a significant difference.

Finally, there is a wide range of drugs and environmental toxins capable of inducing PNs. This involves a long list of compounds and toxins, including drugs, such as vincristine, metronidazole, phenytoin, nitrofurantoin, isoniazid, statins, and organic herbicides, tetrachlorodibenzodioxin (TCDD dioxin), organic metals, heavy metals, and excess intake of vitamin B6 (pyridoxine). In the area of chemotherapy-induced PNs, a number of newer compounds have been found to cause significant damage to peripheral nerves. Such novel agents include bortezomib, a proteasome inhibitor, which is used mostly for the therapy of plasmocytoma. This compound induces a significant predominantly sensory axonal neuropathy, which is dose-limiting. Other recent compounds that cause PNs are employed in breast cancer and include vedotin, mertansine, ixabepilone, and eribulin mesylate, all targeting cellular microtubules [23].

Environmental toxins that may also contribute to the epidemic rise in diabetes are also known to induce PNs [24]. Exposure to several heavy metals, such as lead (lead based paint and lead in gasoline), arsenic (well water contamination), thallium (pesticides), and mercury (contaminated fish, industry) can cause severe forms of PNs [23]. Moreover occupational exposure and/or inhalation of specific toxins including acrylamide, allyl chloride, carbon disulfide, dimethylaminopropionitrile (DMAPN), ethylene oxide, hexacarbons, and organophosphates may be associated with PNs. Although environmental toxins may have decreased in the Western world – which is trying to abide by improved environmental standards – it may be an increasing problem in the rapidly developing countries of Asia and Africa.

The post 9/11 peripheral neuropathy symptoms seen in up to 30 % of the world trade center (WTC)-exposed firefighters and emergency medical service workers, was suggested to be due to a methanol-soluble element in the WTC dust [25].



▶ **Fig. 2** Effect of INUSpheresis® on serum C-reactive protein (sCRP), tumor necrosis factor-alpha(TNF-alpha), Eosinophilic cationic protein (ECP), Regulated And Normal T cell Expressed and Secreted (RANTES). ** indicating a significant difference.

Finally, biological toxins occurring in plankton or fish may enter the food chain. Likewise, ingestions of certain fruits, such as the buckthorn plant, which grows in parts of the US and Mexico, can cause sensorimotor PNs mimicking the Guillain–Barré syndrome. In addition to Lyme disease carried by ixodes genus ticks, other ticks can cause PNs. Some of these ticks may contain neurotoxins in their saliva which might even induce paralysis and breathing problems [23].

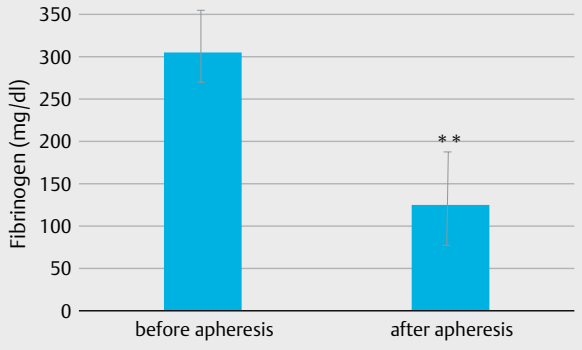
Potential use of therapeutic apheresis

For the majority of PNs, including the most frequent form related to DM there is no specific effective therapy. In the past few years, we have been observing that diabetic PNs is further complicated by an increase of other causatory factors, which may involve not only gluco- and lipotoxicity, but also other metabolic alterations, as well as inflammation and exposure to alcoholic beverages or other toxins. Therefore, it is unlikely that one specific cellular or neuronal pathway will be found that could be the ideal single target for an effective curative therapy.

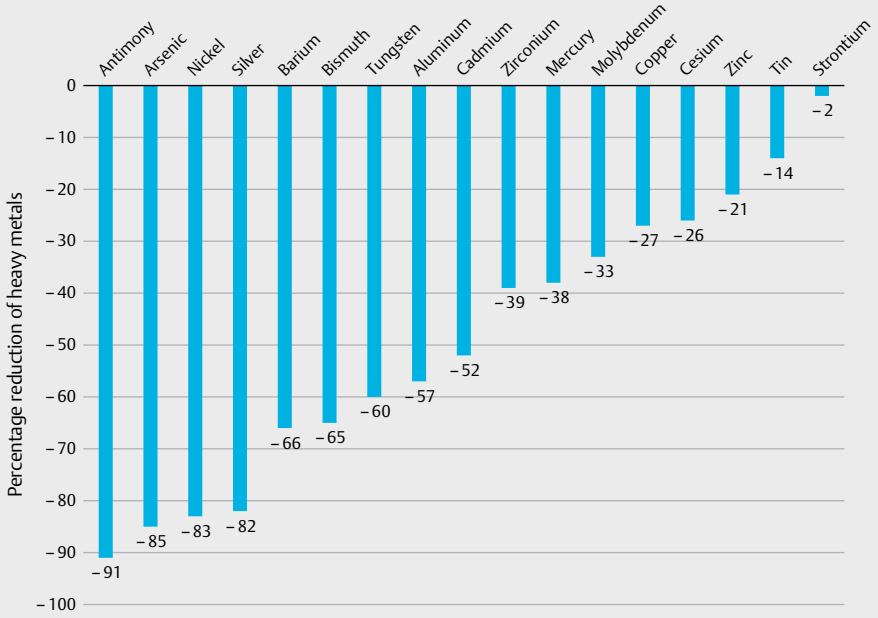
An advantage of therapeutic apheresis is the potential of effective removal of metabolic, inflammatory and toxic components at the same time [26]. In our centers, therapeutic apheresis (INUSpherese®) is established for the treatment of severe lipid and immunologic disorders, and for various intoxications [27–30]. Apheresis has also been applied successfully for the diabetic foot syndrome associated with diabetic PNs [27–29]. In fact, according to the Japanese guidelines, lipoprotein apheresis is a recommended treatment option for patients with diabetic foot syndrome and PNs [31–33]. Similarly, plasma exchange has been widely used in neurological disorders for several specific indications. These include immunadsorption, plasmapheresis for patients with recumbent *neuromyelitis optica* spectrum disorder [34], and for patients with Guillain–Barré syndrome [35], or multiple sclerosis, and paraproteinemia polyneuropathy [36].

Therapeutic apheresis is a standard therapy recommended in guidelines for adults and children with acute relapses of inflammatory demyelinating conditions [37]. For instance, in a patient who presented with hepatitis B-related optic neuritis, high doses of methylprednisolone failed to provide any improvement [38]. However, after 5 sessions of therapeutic plasma exchange, this patient was cured, regaining his visual function [38]. In larger cohorts, plasmapheresis led to functionally important visual recovery in more than 50 % of patients with severe optic neuritis that had failed to respond to glucocorticoids [39].

In the INUS center, we treated with extracorporeal double membrane apheresis more than 500 patients with multi-factorial PNs of unknown origin. Patients were suffering over an extended period of time from severe symptoms of PNs and no prior treatment has provided any benefit. Following apheresis, patients reported a significant improvement of their symptoms. This form of therapeutic apheresis



▶ **Fig. 3** Effect of INUSpheresis® on fibrinogen in patients with polyneuropathy. ** indicating a significant difference.



▶ **Fig. 4** Effect of INUSpheresis® on reduction of heavy metals in patients with polyneuropathy.

(INUSpherese®) caused a reduction of LDL cholesterol and other lipids by more than 50 %, in the same range seen with other methods of lipoprotein apheresis (▶ **Fig. 1**). In the same patients, inflammatory parameters, such as CRP, TNF-alpha, eosinophil cationic protein (ECP), and Regulated And Normal T cell Expressed and Secreted (RANTES) were significantly reduced (▶ **Fig. 2**). There was also a 30–50 % reduction of circulating immunoglobulins, including IgA, IgG, and IgM. Serum fibrinogen concentration was reduced by 60 % (▶ **Fig. 3**), whereas there was only a minor reduction in alpha 2-macroglobulin.

Our apheresis system is efficient in removing environmental toxins. Therefore, in patients with PNs, halogenated carbohydrates, including dichloromethane or tetrachloroethane, or benzene-based solvents, such as ethylbenzene or xylene, and pesticides such as p,p′-DDE, were all reduced by about 50 %. We also observed a significant reduction of other metabolic toxins, such as ethanol, acetone, methanol, and propanol in PNs patients treated with our apheresis system. Likewise, most of the heavy metals that have been implicated in the pathogenesis of PNs were significantly reduced with the INUSpheresis® system (▶ **Fig. 4**).

In conclusion, we suggest that the use of therapeutic apheresis in patients with both metabolic and non-metabolic or combined causes of PNs should be explored in a more extensive manner. If there is a clear-cut cause of PNs including deterioration of glycemic control in diabetic patients or vitamin B12 deficiency, a specific management of these disorders has to be performed. However, given the more common multifunctional and complex pathogenesis of PNs and given the lack of other efficient therapeutic options, and the frequently severe, painful and debilitating consequences of peripheral neuropathy, a more invasive treatment may be justified. Therapeutic apheresis may have the potential of removing a wide variety of pathogenic factors involved in this devastating disease. These include metabolic factors, such as glucose and lipids, inflammatory determinants of the disease process, including CRP, inflammatory cytokines, circulating immune complexes as well as chemical and biological toxins. Randomized controlled assessment of therapeutic apheresis forms the basis for a rapid and sustainable improvement for the increasing number of patients with severe forms of PNs.

Conflict of Interest

Straube R. is employed by the INUS centre. Bornstein SR. and Julius U. have been involved in joint studies with Kaneka, Miltenyi and INUS.

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