Introduction
Idiopathic carpal tunnel syndrome (CTS) is estimated to occur in 1% of the general population, with occasional symptoms noted in as many as 3.7% of adults. As regard to the pathophysiology of idiopathic CTS, a number of studies have carried out to identify tissue alterations typical or consistent to idiopathic carpal tunnel syndrome. Most of them including our own reported that the inflammatory changes are extremely rare, still, there exist connective tissue changes such as edema or fibrosis and vascular changes including vessel wall thickening or even occlusion by thrombi. The purpose of the present study is to carry out a histological, immunohistochemical and biochemical study of the flexor tenosynovium harvested during open carpal tunnel release to determine whether observed vascular changes relate directly to the disease and, if they do, to identify the pathomechanisms behind.

Materials and Methods
Subjects: Written informed consent was obtained from all patients and a standard open carpal tunnel release was performed and the tenosynovium was removed and analyzed. The study was approved by the institutional review board. The study group consisted of 40 patients (12 men and 28 women) and the patients’ mean age was 53.2 years (range, 31 to 79 years). Patients with a history of diabetes mellitus, inflammatory arthritis, autoimmune disorders, thyroid abnormalities, or renal failure, were excluded. The patients were divided into 4 groups based on disease duration. The groups included: group A (< 3 months), group B (group 4 - 6 months), group C (7 -12 months) and group D (>12 month).

Histological analysis: The specimens were embedded in paraffin, cut into 5-um-thick sections, and stained with hematoxylin and eosin (HE) and elastica van-Gieson staining.

Immunohistochemistry: Immunohistochemical studies were performed with a polyclonal anti-MMP2 antibody (Daichi Fine Chemical, Takaoka, Japan).

Gelatin-zymography: The biopsy specimens were quick frozen by liquid nitrogen, homogenized using a Cryopress. Homogenates were separated by electrophoresis and gels were developed by staining Comassic Brilliant Blue. The enzymatic activity was measured by computer assisted image analysis and expressed as (activated MMP2/total MMP2) according to the method of Davies.

Results
Both HE and elastica van-Gieson staining clearly demonstrated that the vessel abnormalities are medial and intimal hyperplasia which occurred mostly in small arteries (Fig. 1, 2). Basically the lesion was similar to proliferative arteriosclerosis seen in diseases such as malignant hypertension, graft-versus-host disease (GVHD) and progressive systemic sclerosis (PSS). However, it lacked perivascular infiltration of inflammatory cells and hyaline thickening of the media. Therefore, we modified quantitative criteria for intimal arteritis of Banff score 4, an internationally developed lesion scoring system to standardize the biopsy interpretation for diagnosis of renal allograft pathology and graded the arterial lesion into 3 grades. As shown in Figure 3, arterial lesion did not show any significant correlation with patients’ age but showed close correlation with symptom duration. This indicated that this is a disease-associated lesion and progresses with disease.

Discussion
It has been well demonstrated that MMP-2 is associated with basement membrane and ECM degradation and engages in vascular restenosis after angioplasty by enhancing migration and proliferation of smooth muscle cells and neointimal formation. As demonstrated clearly by elastica van-Gieson staining in the present study, the lesion primarily occurs in the small arteries and morphologically similar to proliferative arteriosclerosis seen in PSS. A number of studies have demonstrated that the balance between MMPs and tissue inhibitors of metalloproteinase (TIMPs) plays significant role in the development of PSS. Although we did not evaluate activities of TIMP in the present study, imbalance between MMP-2 and its inhibitor may lead to degradation of the basal lamina, which in turn may stimulate abnormal proliferation of both smooth muscle cells and endothelium, resulting in rapidly proliferative arteriosclerosis. Both ischemic and mechanical factors are suggested to involve in compression neuropathy. Accordingly, we think that idiopathic CTS is caused by tenosynovial swelling triggered by arterial lesion from abrupt MMP-2 activation in the tenosynovium. Since carpal tunnel is a confined space composed of carpal bone and flexor retinaculum, tenosynovial swelling leads to interstitial fluid pressure increase, which in turn causes median nerve damage.

References