cholesterol/HDL-cholesterol ratio. Hyperlipidemia per se does not immediately increase arterial wall stiffness. After accumulation of cholesterol in the lipid pool, oxidative stress generates oxysterol, which is highly toxic and enhances inflammation, followed by the onset of atherosclerosis; therefore, CAVI may increase under certain conditions in dyslipidemia.

The effects of lipid-lowering agents have been reported (**Table 2**). Miyashita *et al.*[54] reported that pitavastatin treatment decreased CAVI after one year. Eicosapentaenoic acid reduces CAVI in association with decreased serum amyloid A-LDL in metabolic syndrome[55]. Ezetimibe monotherapy decreases CAVI in type 2 diabetic patients[56]. The arterial stiffness-improving effect of lipid-lowering agents might be due to some functional modulation in addition to organic pathologic changes.

D. Metabolic Syndrome, Obesity and Weight Reduction

Metabolic syndrome prevails worldwide. Visceral fat accumulation has been suggested to induce glucose intolerance, hypertension, and dyslipidemia, such as low HDL-cholesterol and hypertriglyceridemia[57]. These conditions are believed to be due to insulin resistance. High CAVI is associated with obesity and metabolic syndrome[58]. Adiponectin, which is implicated in insulin sensitivity and considered to be a biomarker of metabolic syndrome, is related negatively to CAVI[59]. The above findings indicate that CAVI could be a good marker of macroangiopathy in metabolic syndrome, for which there are few initial signs and symptoms.

Weight reduction is known to improve metabolic syndrome, and Satoh *et al.*[58] reported that weight reduction through diet and exercise therapy over a 3-month period significantly decreased CAVI values in parallel with increasing adiponectin. CAVI may be useful for evaluating and managing the cardiovascular risks of patients with metabolic syndrome.

E. Sleep Apnea Syndrome

CAVI has been reported to be high in sleep apnea syndrome[60] and to decrease with continuous positive airway pressure (CPAP)[61]. The mechanism by which CAVI increases in sleep apnea syndrome may be due to the activation of sympathetic nerves by sleep apnea, which consequently increases arterial wall stiffness.

Interestingly, since CAVI decreases after CPAP therapy in patients with sleep apnea syndrome, CAVI could be used as an efficient marker for CPAP therapy.

F. Smoking

Kubozono *et al.*[21] reported that CAVI was high in smoking subjects. Noike *et al.*[62] reported that smoking increases CAVI but, interestingly, CAVI decreases after stopping smoking. This reversible change of CAVI might imply that smoking contracts the arterial wall of smooth muscle cells. CAVI may be a good indicator to enhance the motivation of persons who are trying to stop smoking.

G. CAVI in Inflammatory Vascular Disease

Inflammatory diseases of the arterial wall are known to be associated with accelerated atherosclerosis. Detection of increased arterial stiffness in patients in the early stage of large vessel vasculitis may be possible by measuring CAVI. Recent case reports showed that CAVI was high in patients with systemic lupus erythematosis[63] and aortitis syndrome[64, 65], and the augmented CAVI was decreased by immunosuppressive therapy[65]. These results indicate that CAVI reflects the presence of an inflammatory reaction of arteries in the whole body. The mechanism by which CAVI increases in such conditions is not known. Inflammatory cytokines generated in the arterial wall might induce the contraction of smooth muscle cells or induce remodeling of the arterial wall, but detailed studies on these issues are required. Wakabayashi *et al.*[66] reported that CAVI is associated with acute phase reactants, such as C-reactive protein, amyloid A protein, sialic acid, fibrinogen and white blood cells in type 2 diabetes mellitus.

H. Miscellaneous Diseases and/or Conditions

Besides arteriosclerosis-related disorders, CAVI is changed in many diseases and/or conditions. Torisu *et al.*[67] reported that CAVI was significantly higher in atrophic gastritis-positive patients than in atrophic gastritis-negative patients, even after adjusting for possible confounding factors (8.59 ± 1.20 vs. 8.27 ± 1.19 $p = 0.022$).

Wu *et al.*[68] reported that personal exposure to ozone was associated with a 4.8% increase in CAVI, suggesting that vascular function may be more sensitive to air pollutants. Those reports may indicate that many unidentified factors involved in the development of arteriosclerosis could be evaluated using CAVI in the future.

Relationship between CAVI and Cardiac Functions

Mizuguchi[69] reported that arterial stiffness is associated with left ventricular diastolic function in

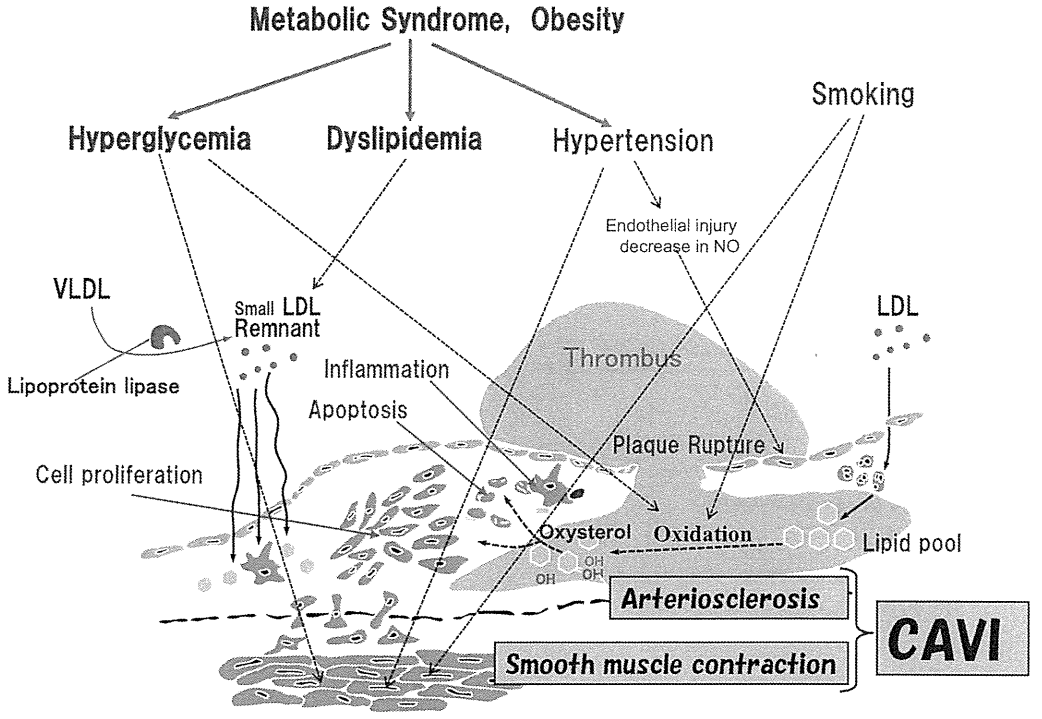

Fig. 6. Atheroma formation with coronary risk factors and CAVI.

The process of athero- and arteriosclerosis is supposed as follows. A lipid pool is formed with infiltration of LDL, small dense LDL and remnants. Oxidation of lipids provokes inflammation. Then, smooth muscle cells proliferate to form intimal thickening. Inflammatory reaction gathers macrophages, which degrade the matrix, and also induce smooth cell apoptosis. Then, plaque rupture occurs and thrombus is formed.
Risk factors are involved in various steps. Some target the endothelial cells and produce injuries. Some promote oxidation stress in the arterial wall. Others target medial smooth muscle cells, increasing contraction or provoking cell proliferation. Interestingly, all these injurious reactions seem to be integrated in CAVI.

patients with cardiovascular risk factors. They demonstrated that CAVI correlated positively with peak early diastolic trans-mitral flow velocity, E/A, and the deceleration time of early diastolic transmitral flow velocity (E-DT). Sakane *et al.*[70] showed that CAVI was significantly higher in patients with reduced left ventricular (LV) diastolic function than in those with normal LV diastolic function (9.0 ± 1.1 versus 8.5 ± 1.1, $p = 0.009$), and concluded that increased CAVI is independently associated with LV diastolic dysfunction in patients with preserved systolic function. Masugata *et al.*[71] measured the peak early diastolic mitral annular velocity (E') as an index of LV diastolic function using tissue Doppler echocardiography, and demonstrated that E' correlates with CAVI ($r = -0.518$, $p < 0.001$). They also reported that aortic annular velocity assessed by tissue Doppler echocardiography is a potential parameter of arterial stiffness[72]. These results indicate that left ventricular diastolic function correlates with vascular elasticity indicated by CAVI. In other words, the state of high CAVI of the elastic and muscular arterial wall might worsen left ventricle diastolic function; therefore, measuring CAVI may be important when considering diagnostic and therapeutic strategies aiming at cardiac protection[69, 70]. Further investigations are needed to confirm a causal relationship.

Summary

What is CAVI? What is the Outlook of CAVI a Marker of Arteriosclerosis?

A high CAVI is observed in many arteriosclerotic diseases, such as coronary artery disease, carotid arteriosclerosis, chronic kidney disease and cerebrovascular disease, and is related to many coronary risk factors, such as hypertension, diabetes mellitus, dyslipidemia and smoking, as shown in **Table 1**. These clinical data indicate that CAVI can be a surrogate marker of athero- or arteriosclerosis. Furthermore, CAVI decreases in a relatively short period by various treatments, as shown in **Table 2**. Furthermore, vasodilators such as doxazosin and α1- aderenergic receptor

Table 3. Cardiac Function and CAVI

Left ventricular diastolic function	CAVI value	Reference
Left ventricular ejection fraction	→	Sakane[70], Mizuguchi[69]
Left atrial dimension	↑	Sakane[70], Mizuguchi[69]
Peak early diastolic velocity (E)	↑	Sakane[70], Mizuguchi[69], Masugata[71]
Peak atrial diastolic velocity (A)	↑	Sakane[70]
E/A	↑	Sakane[70], Mizuguchi[69]
Deceleration time of E velocity (DcT)	→	Sakane[70], Mizuguchi[69]

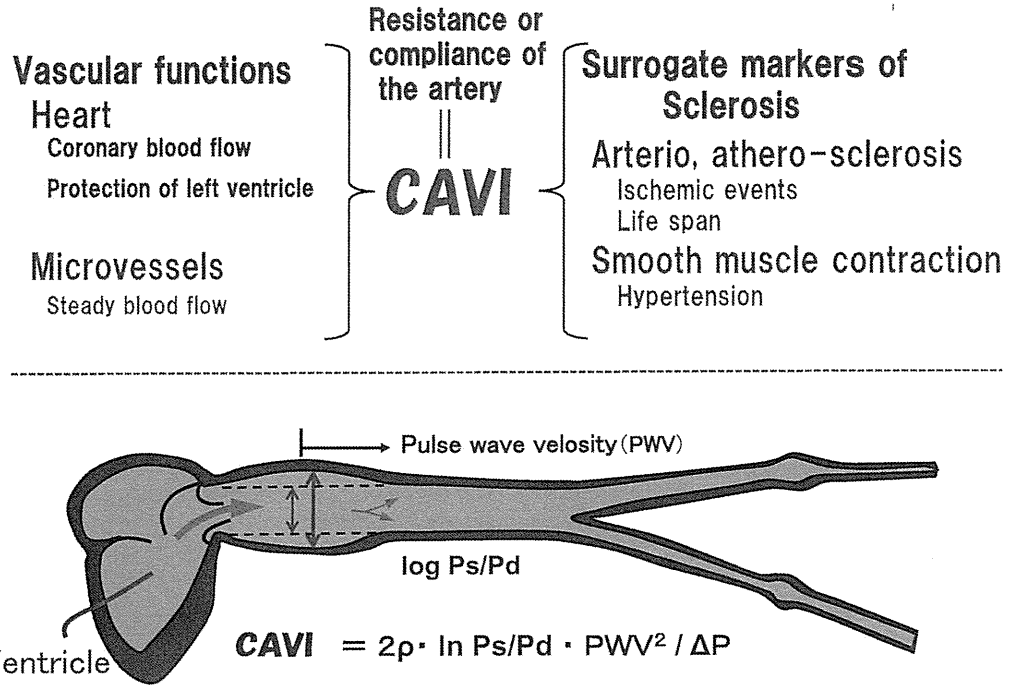

Fig. 7. Roles of CAVI in resistance or compliance of the artery as a surrogate marker of arteriosclerosis and also vascular function.

CAVI reflects the resistance or compliance of the artery; therefore, CAVI indicates the degree of sclerosis of the artery, and also reflects vascular function which keeps the heart functioning and maintains peripheral steady blood flow as a Windkessel. The former is a surrogate marker of arteriosclerosis and smooth muscle contraction. The latter might protect or improve left ventricular function, and maintain steady blood flow. To confirm this, many more basic and clinical studies are required.

blocker decrease CAVI in 1 to 5 hours, concomitant with a decrease in blood pressure (**Fig. 3B**, Ref. 23), indicating that smooth muscle cell contraction is an important determinant of CAVI, in addition to the organic components of the arterial wall, summarized in **Fig. 6**.

Many risk factors, such as hyperglycemia, hypertension, dyslipidemia (small dense LDL, remnants, LDL) and smoking, act injuriously on the arterial wall in their own ways, including endothelial dysfunction, oxidative stress and provoking inflammation. One method is by promoting organic sclerosing process and an other is by promoting the contraction of smooth muscle cells. Both processes might be integrated into CAVI.

In the future, CAVI might be useful to compare the severity of arteriosclerosis in people in different districts or countries, and might be useful to find risk

factors in each[73, 74]. CAVI might also be a good physiological surrogate marker of lifestyle change, such as ceasing smoking, control of blood pressure and glucose level, and resultantly might be expected to contribute to the prevention of arteriosclerotic diseases.

As a Marker of Vascular Function

The circulation system is composed of the heart, large- and medium-sized arteries and microvessels. Pulsatile movement of the heart efficiently transports the blood to peripheral organs with the aid of vascular function; that is, the arteries dilate in the systolic phase and contract during the diastolic phase. While this windkessel action is ascribed to vascular compliance or resistance[1], an index to reflect this function has not been available. Several reports have confirmed that CAVI and left ventricular functions are related, as shown in **Table 3**[69-71]. Furthermore, the α1-aderenergic receptor blocker doxazosin, which dilates the peripheral arteries by decreasing resistance, decreases CAVI as described above[23]. These results indicate that CAVI reflects the compliance or resistance of the artery, and may have a protective effect on the left ventricle, as shown in **Fig. 7** (lower panel).

The possibility that CAVI plays a role in the analysis of systemic circulation as a marker of peripheral resistance or compliance deserves to be evaluated. In this context, CAVI may open a new field in the study of systemic circulation.

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References

1) Asmar R: Pulse wave velocity principles and measurement 25-55. In: Arterial stiffness and pulse wave velocity, edited by Asmar R, O'Rourke MF, Safar M. Elsevier, Amsterdam, 1999
2) Oliver JJ, Webb DJ: Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. Arterioscler Thromb Vasc Biol, 2003; 23: 554-566
3) Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, Witteman JC: Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation, 2006; 113: 657-663
4) O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE: Clinical applications of arterial stiffness; definitions and reference values. Am J Hypertens, 2002; 15: 426-444
5) Koizumi M, Shimizu H, Shimomura K, Oh-I S, Tomita Y, Kudo T, Iizuka K, Mori M: Relationship between hyperinsulinemia and pulse wave velocity in moderately hyperglycemic patients. Diabetes Res ClinPr, 2003; 62: 17-21
6) Avest E, Holewijn S, Bredie SJ, van Tits LJ, Stalenhoef AF, de Graaf J: Pulse wave velocity in familial combined hyperlipidemia. Am J Hypertens, 2007; 20: 263-269
7) Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, Tomiyama H, Yamashina A, Yasuda H, Sawayama T, Ozawa T: Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. J Hypertens, 2009; 27: 2022-2027
8) Lemogoum D, Flores G, Van den Abeele W, Ciarka A, Leeman M, Degaute JP, van de Borne P, Van Bortel L: Validity of pulse pressure and augmentation index as surrogate measures of arterial stiffness during beta-adrenergic stimulation. J Hypertens, 2004; 2: 511-517
9) Hayashi K, Handa H, Nagasawa S, Okumura A, Moritake K: Stiffness and elastic behavior of human intracranial and extracranial arteries. J Biomech, 1980; 13: 175-184
10) Kawasaki T, Sasayama S, Yagi S: Noninvasive assessment of the age related changes in stiffness of major branches of the human arteries. Cardiovascular Res, 1987; 21: 678-687
11) Frank O: Die Theorie der Pulswellen. Zeitschrift fur Biologie, 1926; 85: 91-130
12) Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Koji Y, Hori S, Yamamoto Y: Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res, 2002; 25: 359-364
13) Kim HJ, Nam JS, Park JS, Cho M, Kim CS, Ahn CW, Kwon HM, Hong BK, Yoon YW, Cha BS, Kim KR, Lee HC: Usefulness of brachial-ankle pulse wave velocity as a predictive marker of multiple coronary artery occlusive disease in Korean type 2 diabetes patients. Diabetes Res Clin Pr, 2009; 85: 30-34
14) Nye ER: The effect of blood pressure alteration on the pulse wave velocity. Br Heart J, 1964; 266: 261-265
15) Hasegawa M: Fundamental research on human aortic pulse wave velocity. Jikei Medical Journal, 1970; 85: 742-760
16) Hamazaki T, Urakaze M, Sawazaki S, Yamazaki K, Taki H, Yano S: Comparison of pulse wave velocity of the aorta between inhabitants of fishing and farming villages in Japan. Atherosclerosis, 1988; 73: 157-160
17) Saito Y, Shirai K, Utino J, Okazaki M, Hattori Y, Yoshida T, Yoshida S: Effect of nefedipine administration on pulse wave velocity of chronic hemodialysis patients- 2 years trial. Cardiovas Drug Ther, 1990; 4: 987-990
18) Shirai K, Utino J, Otsuka K, Takata M: A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb,

2006; 13: 101-107
19) Bramwell JC, Hill AV: Velocity of the pulse wave in man. Proc Roy Soc, 1922; B: 298-306
20) Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Matsuda T, Hiratsuka A, Matsuzaki M: Cardio-ankle vascular index is a new noninvasive parameter of arterial stiffness. Circ J, 2007; 71: 1710-1714
21) Kubozono T, Miyata M, Ueyama K, Nagaki A, Otsuji Y, Kusano K, Kubozono O, Tei C: Clinical significance and reproducibility of new artrial dstensibility index. Circ J, 2007; 71: 89-94
22) Ibata J, Sasaki H, Kakimoto T, Matsuno S, Nakatani M, Kobayashi M, Tatsumi K, Nakano Y, Wakasaki H, Furuta H, Nishi M, Nanjo K: Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. Diabetes Res Clin Pr, 2008; 80: 265-270
23) Shirai K, Song M, Suzuki J, Kurosu T, Oyama T, Nagayama D, Miyashita Y, Yamamura S, Takahashi M: Contradictory effects of β1- and α1- aderenergic receptor blockers on cardio-ankle vascular stiffness index (CAVI) -the independency of CAVI from blood pressure. J Atheroscler Thromb, 2011; 18: 49-55
24) Nakamura K, Tomaru T, Yamamura S, Miyashita Y, Shirai K, Noike H: Cardio-ankle vascular index is a candidate predictor of coronary atherosclerosis. Circ J, 2008; 72: 598-604
25) Izuhara M, Shioji K, Kadota S, Baba O, Takeuchi Y, Uegaito T, Mutsuo S, Matsuda M: Relationship of cardio-ankle vascular index (CAVI) to carotid and coronary artery sclerosis. Circ J, 2008; 72: 1762-1767
26) Miyoshi T, Doi M, Hirohata S, Sakane K, Kamikawa S, Kitawaki T, Kaji Y, Kusano KF, Ninomiya Y, Kusachi S: Cardio-ankle vascular index is independently associated with the severity of coronary atherosclerosis and left ventricular function in patients with ischemic heart disease. J Atheroscler Thromb, 2010; 17: 249-258
27) Horinaka S, Yabe A, Yagi H, Ishimura K, Hara H, Iemua T, Matsuoka H: Comparison of atherosclerotic indicators between cardio ankle vascular index and brachial ankle pulse wave velocity. Angiology, 2009; 60: 468-476
28) Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Hiratsuka A, Matsuzaki M: Cardio-ankle vascular index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res, 2008; 31: 1347-1355
29) Sairaku A, Eno S, Hondo T, Teragawa H, Nakano Y, Matsuda K, Kisaka T, Kihara Y: Head-to-head comparison of the cardio-ankle vascular index between patients with acute coronary syndrome and stable angina pectoris. Hypertens Res, 2010; 33: 1162-1166
30) Kubozono T, Miyata M, Ueyama K, Nagaki A, Hamasaki S, Kusano K, Kubozono O, Tei C: Association between arterial stiffness and estimated glomerular filtration rate in the Japanese general population. J Atheroscler Thromb, 2009; 16: 840-845
31) Takenaka T, Hoshi H, Kato N, Kobayashi K, Takane H, Shoda J, Suzuki H: Cardio-ankle vascular index to screen cardiovascular diseases in patients with end-stage renal diseases. J Atheroscler Thromb, 2008; 15: 339-344
32) Nakamura K, Iiduka T, Takahashi M, Shimizu S, Mikamo H, Nakagami T, Suzuki M, Hirano K, Sugiyama Y, Tomaru T, Miyashita Y, Shirai K, Noike H: Association between cardio-ankle vascular index and serum cystain c levels in patients with cardiovascular risk factor. J Atheroscler Thromb, 2009; 16: 371379-370
33) Ueyama K, Miyata M, Kubozono T, Nagaki A, Hamasaki S, Ueyama S, Tei C: Noninvasive indices of arterial stiffness in hemodialysis patients. Hypertens Res, 2009; 32: 716-720
34) Ichihara A, Yamashita N, Takemitsu T, Kaneshiro Y, Sakoda M, Kurauchi-Mito A, Itoh H: Cardio-ankle vascular index and ankle pulse wave velocity as a marker of arterial fibrosis in kidney failure treated by hemodialysis. Am J Kidney Dis, 2008; 52: 947-955
35) Shen TW, Wang CH, Lai YH, Hsu BG, Liou HH, Fang TC: Use of cardio-ankle vascular index in chronic dialysis patients. Eur J Clin Invest, 2011; 41: 45-51
36) Satoh-Asahara N, Suganami T, Majima T, Kotani K, Kato Y, Araki R, Koyama K, Okajima T, Tanabe M, Oishi M, Himeno A, Kono, Sugawara A, Hattori M, Ogawa Y, Shimatsu, A and the Japan Obesity and Metabolic Syndrome Study (JOMS) Group Urinary Cystatin C as a Potential Risk Marker for Cardiovascular Disease and Chronic Kidney Disease inPatients with Obesity and Metabolic Syndrome. Clin J Am Soc Nephrol, 2011; 6: 265-273
37) Okura T, Watanabe S, Kurata M, Manabe S, Koresawa M, Irita J, Enomoto D, Miyoshi K, Fukuoka T, Higaki J: Relationship between cardio-ankle vascular index (CAVI) and carotid atherosclerosis in patients with essential hypertension. Hypertens Res, 2007; 30: 335-340
38) Hayashi S: Significance of plasma D-dimer in relation to the severity of atherosclerosis among patients evaluated by non-invasive indices of cardio-ankle vascular index and carotid intima-media thickness. Int J Hematol, 2010; 92: 76-82
39) Yamamoto N, Yamanaka G, Ishikawa M, Takasugi E, Murakami S, Yamanaka T, Ishine M, Matsubayashi K, Hanafusa T, Otsuka K: Cardio-ankle vascular index as a predictor of cognitive impairment in community-dwelling elderly people: four-year follow-up. Dement Geriatr Cogn Disord, 2009; 28: 153-158
40) Kato A, Takita T, Furuhashi M, Kumagai H, Hishida A: A small reduction in the ankle-brachial index is associated with increased mortality in patients on chronic hemodialysis. Nephron Clin Pract, 2010; 114: c29-37
41) Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Matsuda T, Hiratsuka A, Matsuzaki M: Cardio-ankle vascular index is a new noninvasive parameter of arterial stiffness. Circ J, 2007; 71: 1710-1714
42) Kadota K, Takamura N, Aoyagi K, Yamasaki H, Usa T, Nakazato M, Maeda T, Wada M, Nakashima K, Abe K, Takeshima F, Ozono Y: Availability of cardio-ankle vascular index (CAVI) as a screening tool for atherosclerosis. Circ J, 2008; 72: 304-308
43) Masugata H, Senda S, Himoto T, Okuyama H, Inukai M, Murao K, Hosomi N, Yukiiri K, Kohno M, Yamagami A, Kohno T, Goda F: Early detection of hypertension in a patient treated with sunitinib by measuring cardio-ankle

vascular index. Tohoku J Exp Med, 2009; 218: 115-119
44) Uehara G, Takeda H: Relative effects of telmisartan, candesartan and losartan on alleviating arterial stiffness in patients with hypertension complicated by diabetes mellitus: an evaluation using the cardio-ankle vascular index (CAVI). J Int Med Res, 2008; 36: 1094-1102
45) Kinouchi K, Ichihara A, Sakoda M, Kurauchi-Mito A, Murohashi-Bokuda K, Itoh H: Effects of telmisartan on arterial stiffness assessed by the cardio-ankle vascular index in hypertensive patients. Kidney Blood Press Res, 2010; 33: 304-312
46) Bokuda K, Ichihara A, Sakoda M, Mito A, Kinouchi K, Itoh H: Blood pressure-independent effect of candesartan on cardio-ankle vascular index in hypertensive patients with metabolic syndrome. Vasc Health Risk Manag, 2010; 6: 571-578
47) Sasaki H, Saiki A, Endo K, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohhira M, Oyama T, Miyashita Y, Shirai K: Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy. J Atheroscler Thromb, 2009; 16: 568-575
48) Miyashita Y, Saiki A, Endo K, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohira M, Oyama T, Shirai K: Effects of olmesartan, an angiotensin II receptor blocker, and amlodipine, a calcium channel blocker, on Cardio-Ankle Vascular Index (CAVI) in type 2 diabetic patients with hypertension. J Atheroscler Thromb, 2009; 16: 621-626
49) Ishimitsu T, Numabe A, Masuda T, Akabane T, Okamura A, Minami J, Matsuoka H: Angiotensin-II receptor antagonist combined with calcium channel blocker or diuretic for essential hypertension. Hypertens Res, 2009; 32: 962-968
50) Kinouchi K, Ichihara A, Sakoda M, Kurauchi-Mito A, Itoh H: Safety and benefits of a tablet combining losartan and hydrochlorothiazide in Japanese diabetic patients with hypertension. Hypertens Res, 2009; 32: 1143-1147
51) Nagayama D, Saiki A, Endo K, Yamaguchi T, Ban N, Kawana H, Ohira M, Oyama T, Miyashita Y, Shirai K: Improvement of cardio-ankle vascular index by glimepiride in type 2 diabetic patients. Int J Clin Pract, 2010; 64: 1796-1801
52) Ohira M, Endo K, Oyama T, Yamaguchi T, Ban N, Kawana H, Nagayama D, Nagumo A, Saiki A, Murano T, Watanabe H, Miyashita Y, Shirai K: Improvement of postprandial hyperglycemia and arterial stiffness upon switching from premixed human insulin 30/70 to biphasic insulin aspart 30/70. Metabolism, 2010; 60: 78-85
53) Takaki A, Ogawa H, Wakeyama T, Iwami T, Kimura M, Hadano Y, Matsuda S, Miyazaki Y, Hiratsuka A, Matsuzaki M: Cardio-ankle vascular index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res, 2008; 31: 1347-1355
54) Miyashita Y, Endo K, Saiki A, Ban N, Yamaguchi T, Kawana H, Nagayama D, Ohira M, Oyama T, Shirai K: Effects of pitavastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, on cardio-ankle vascular index in type 2 diabetic patients. J Atheroscler Thromb, 2009; 16: 539-545
55) Satoh N, Shimatsu A, Kotani K, Himeno A, Majima T, Yamada K, Suganami T, Ogawa Y: Highly purified eicosapentaenoic acid reduces cardio-ankle vascular index in association with decreased serum amyloid A-LDL in metabolic syndrome. Hypertens Res, 2009; 32: 1004-1008
56) Miyashita Y, Endo K, Saiki A, Ban N, Nagumo A, Yamaguchi T, Kawana H, Nagayama D, Ohira M, Oyama T, Shirai K: Effect of ezetimibe monotherapy on lipid metabolism and arterial stiffness assessed by cardio-ankle vascular index in type 2 diabetic patients. J Atheroscler Thromb, 2010; 17: 1070-1076
57) Shirai K: Obesity as the core of the metabolic syndrome and the management of coronary heart disease. Curr Med Res Opin, 2004; 20: 295-304
58) Satoh N, Shimatsu A, Kato Y, Araki R, Koyama K, Okajima T, Ooshim M,Kotani K, Ogawa Y: Evaluation of the cardio-ankle vascular index, anew indicator of arterial stiffness independent of blood pressure, inobesity and metabolic syndrome. Hypertention Res, 2008; 31: 1921-1930
59) Ohashi N, Ito C, Fujikawa R, Yamamoto H, Kihara Y, Kohno N: The impact of visceral adipose tissue and high-molecular weight adiponectin on cardio-ankle vascular index in asymptomatic Japanese subjects. Metabolism, 2009; 58: 1023-1029
60) Kumagai T, Kasai T, Kato M, Naito R, Maeno K, Kasagi S, Kawana F, I, Shiwata S, Narui K: Establishment of the cardio-ankle vascular index in patients with obstructive sleep apnea. Chest, 2009; 136: 779-786
61) Lü YH, He ZM, Dong XS, Li J, Han X, An P, Wang L, He QY, Han F: Effects of short-term continuous positive airway pressure treatment on arterial stiffness in patients with obstructive sleep apnea hypopnea syndrome. Zhonghua Yi Xue Za Zhi, 2008; 88: 1189-1191
62) Noike H, Nakamura K, Sugiyama Y, Iizuka T, Shimizu K, Takahashi M, Hirano K, Suzuki M, Mikamo H, Nakagami T, Shirai K: Changes in cardio-ankle vascular index in smoking cessation. J Atheroscler Thromb, 2010; 17: 517-525
63) Sato H, Miida T, Wada Y, Maruyama M, Murakami S, Hasegawa H, Kuroda T, Narita I, Nakano M, Gejyo F: Atherosclerosis is accelerated in patients with long-term well-controlled systemic lupus erythematosus (SLE). Clin Chim Acta, 2007; 385: 35-42
64) Masugata H, Senda S, Himoto T, Murao K, Dobashi H, Kitano Y, Okuyama H, Inukai M, Hosomi N, Kohno M, Nishiyama Y, Kohno T, Goda F: Detection of increased arterial stiffness in a patient with early stage of large vessel vasculitis by measuring cardio-ankle vascular index. Tohoku J Exp Med, 2009; 219: 101-105
65) Masugata H, Senda S, Dobashi H, Himoto T, Murao K, Okuyama H, Inukai M, Hosomi N, Kohno M, Nishiyama Y, Kohno T, Goda F: Cardio-ankle vascular index for evaluating immunosuppressive therapy in a patient with aortitis syndrome. Tohoku J Exp Med, 2010; 222: 77-81
66) Wakabayashi I, Masuda H: Association of acute-phase reactants with arterial stiffness in patients with type 2 diabetes mellitus. Clin Chim Acta, 2006; 365: 230-235
67) Torisu T, Takata Y, Ansai T, Matsumoto T, Sonoki K, Soh I,

Awano S, Yoshida A, Hamasaki T, Kagiyama S, Nakamichi I, Ohsumi T, Toyoshima K, Nishihara T, Iida M, Takehara T: Possible association of atrophic gastritis and arterial stiffness in healthy middle-aged Japanese. J Atheroscler Thromb, 2009; 16: 691-697

68) Wu CF, Kuo IC, Su TC, Li YR, Lin LY, Chan CC, Hsu SC: Effects of personal exposure to particulate matter and ozone on arterial stiffness and heart rate variability in healthy adults. Am J Epidemiol, 2010; 171: 1299-1309

69) Mizuguchi Y, Oishi Y, Tanaka H, Miyoshi H, Ishimoto T, Nagase N, Oki T: Arterial stiffness is associated with left ventricular diastolic function in patients with cardiovascular risk factors: early detection with the use of cardio-ankle vascular index and ultrasonic strain imaging. J Card Fail, 2007; 13: 744-751

70) Sakane K, Miyoshi T, Doi M, Hirohata S, Kaji Y, Kamikawa S, Ogawa H, Hatanaka K, Kitawaki T, Kusachi S, Yamamoto K: Association of new arterial stiffness parameter, the cardio-ankle vascular index, with left ventricular diastolic function. J Atheroscler Thromb, 2008; 15: 261-268

71) Masugata H, Senda S, Goda F, Yamagami A, Okuyama H, Kohno T, Hosomi N, Yukiiri K, Noma T, Kiyomoto H, Murao K, Nishiyama A, Kohno M: Tissue Doppler echocardiography for predicting arterial stiffness assessed by cardio-ankle vascular index. Tohoku J Exp Med, 2009; 217: 139-146

72) Masugata H, Senda S, Okuyama H, Murao K, Hosomi N, Inukai M, Iwado Y, Noma T, Kohno M, Goda F: Aortic annular velocity assessed by tissue Doppler echocardiography as a potential parameter of arterial stiffness. Tohoku J Exp Med, 2010; 221: 169-174

73) Uurtuya S, Taniguchi N, Kotani K, Yamada T, Kawano M, Khurelbaatar N, Itoh K, Lkhagvasuren T: Comparative study of the cardio-ankle vascular index and ankle-brachial index between young Japanese and Mongolian subjects. Hypertens Res, 2009; 32: 140-144

74) Uurtuya S, Kotani K, Taniguchi N, Yoshioka H, Kario K, Ishibashi S, Yamada T, Kawano M, Khurelbaatar N, Itoh K, Lkhagvasuren T: Comparative study of atherosclerotic parameters in Mongolian and Japanese patients with hypertension and diabetes mellitus. J Atheroscler Thromb, 2010; 17: 181-188

ORIGINAL PAPER

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Improvement of cardio-ankle vascular index by glimepiride in type 2 diabetic patients

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The authors state that they have no interests that might be perceived as posing a conflict or bias.

SUMMARY

Aims: Glimepiride, a third generation sulfonylurea (SU), is known to have extra-pancreatic effects, but its vascular effect is unclear. We investigated the efficacy of glimepiride in improving arterial stiffness assessed by cardio-ankle vascular index (CAVI) in type 2 diabetic patients, compared with glibenclamide, a conventional SU. **Methods:** Forty type 2 diabetic patients were randomly assigned to two groups. One group was administered glimepiride 1.5 mg/day, and the other group was administered glibenclamide 1.25 mg/day for 6 months. **Results:** No significant difference in hypoglycaemic effect was observed between two groups. CAVI significantly decreased only in glimepiride group ($9.4 \pm 1.4 \rightarrow 8.9 \pm 0.8$, $p < 0.05$). Decrease in CAVI was greater in glimepiride group than in glibenclamide group (-0.50 ± 0.98 vs. -0.04 ± 0.57, $p = 0.048$). Urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) decreased in glimepiride group and increased in glibenclamide group, and the changes were significantly different between groups (-1.5 ± 3.5 vs. $+ 1.8 \pm 3.6$, $p = 0.009$); whereas serum lipoprotein lipase mass increased in glibenclamide group and decreased in glibenclamide group, and the changes tended to be different between groups ($+ 2.1 \pm 19.1$ vs. -7.4 ± 19.2, $p = 0.096$). Change in urinary 8-OHdG was a significant independent predictor for change in CAVI in all subjects. **Conclusions:** These results suggest that glimepiride improves CAVI compared with glibenclamide. Reduced oxidative stress and improved insulin resistance may contribute to the improvement of CAVI by glimerpiride.

What's known
Diabetes mellitus is a risk factor for all manifestations of atherosclerotic vascular disease.

What's new
Glimepiride, a third generation sulfonylurea, improves arterial stiffness assessed by CAVI compared with glibenclamide, a conventional sulfonylurea.

Introduction

Diabetes mellitus is a risk factor for all manifestations of atherosclerotic vascular disease, coronary artery disease (CAD), cerebrovascular disease and peripheral vascular disease. The incident of CAD is significantly higher in diabetic patients than in non-diabetic patients (1,2). Insulin resistance in type 2 diabetes is associated with systemic oxidative stress, and this association may result in vascular dysfunction and atherosclerotic vascular disease (3–5).

Glimepiride, a third generation sulfonylurea (SU), exerts its effects mainly by stimulating insulin secretion. Moreover, it has also been shown to have extra-pancreatic actions and pleiotropic effects. For example, recent clinical studies showed glimepiride to enhance insulin sensitivity compared with conventional SUs (6–9). Glimepiride has also been demonstrated to inhibit the formation of atheromatous plaques in thoracic aortae of high-cholesterol fed rabbits (10). However, the efficacy of glimepiride on vascular dysfunction compared with conventional SUs remains unknown.

Recently, a novel arterial stiffness parameter called cardio-ankle vascular index (CAVI) has been developed in Japan, which essentially reflects the stiffness of the aorta, femoral artery and tibial artery (11). CAVI is independent of blood pressure and has adequate reproducibility for clinical use (11). Furthermore, no special technique is required for the measurement of CAVI. Several reports have demonstrated the usefulness of CAVI for the detection of atherosclerotic disease (11–14).

In this study, we investigated the effect of glimepiride on arterial stiffness assessed by CAVI compared with glibenclamide, a conventional SU, in type 2 diabetic patients.

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Subjects and methods

Subjects

A randomised, open study was performed. Outpatients of Sakura Medical Center of Toho University who had poorly controlled type 2 diabetes mellitus and had not been treated with SUs for at least 3 months were eligible. Patients were excluded if they received insulin therapy or had severe diabetic retinopathy, nephropathy and previous cardiovascular and cerebrovascular diseases. Eventually, 40 patients with inadequate glycemic control (glycosylated haemoglobin, HbA1c > 6.5%) and not treated with SUs for the latest 3 months were enrolled. The enrolled subjects were randomly assigned to two groups. Randomisation was carried out with sequentially numbered, sealed envelopes using predetermined codes for either glimepiride or glibenclamide. One group was administered glimepiride 1.5 mg/day (glimepiride group, $n = 20$), and the other group was administered glibenclamide 1.25 mg/day (glibenclamide group, $n = 20$) for 6 months. These drugs were taken in the morning after 12 h of fasting. During this study, all patients maintained the same diet and exercise therapies and did not change medications. All subjects received nutrition guidance from a dietitian every month. This study was approved by the institutional review board. The purpose of this study was explained to the subjects, and the content was obtained for participation in the study and also for the release of the study data.

Measurements

Body weight (BW) was measured in the morning after 12 h of fasting. Blood samples were collected in the morning after 12 h of fasting and before taking glimepiride or glibenclamide. Serum was separated within 1 h, and samples were used for measuring fasting plasma glucose (FPG), HbA1c, basal immuno-reactive insulin (IRI), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and lipoprotein lipase (LPL) mass.

Cardio-ankle vascular index was measured using a VaSera CAVI instrument (Fukuda Denshi Co. Ltd., Tokyo, Japan) by the methods described previously (11). Measurements of CAVI were performed in the morning after 12 h of fasting and before taking glimepiride or glibenclamide. Briefly, with the subject supine and the head in midline position, cuffs were applied to bilateral upper arms and ankles. After resting for 10 min, the examinations were performed. To detect the brachial and ankle pulse waves with cuffs, a low cuff pressure from 30 to 50 mmHg was used to ensure minimal effect of cuff pressure on haemodynamics. Blood pressure was measured thereafter. CAVI was calculated by the following formula: $\mathrm{CAVI} = a\{(2\rho/\Delta P) \times \ln(P_s/P_d)\mathrm{PWV}^2\} + b$; where P_s is systolic blood pressure, P_d is diastolic pressure, PWV is pulse wave velocity, ΔP is $P_s - P_d$, ρ is blood density and a and b are constants.

Scale conversion was performed to compare CAVI with PWV (Hasegawa's method). The VaSera was equipped with both measurement and calculation systems, and automatically calculated the CAVI. The average coefficient of variation of CAVI is < 5%, which is small enough for clinical usage and indicates that CAVI has good reproducibility (11).

Assays of HbA1c and serum lipids

HbA1c, including stable and unstable fractions, was measured by high pressure liquid chromatography using the Hi-Auto A1c kit (Kyoto Daiichi Kagaku, Kyoto, Japan). Data of the stable type were used in the present analysis. TC, TG and LDL-C were measured with an automatic analyser (Hitachi 7150 available from Hitachi, Tokyo, Japan). HDL-C was measured by the selective inhibition method [Daiichi Pure Chemicals, Tokyo, Japan (15)].

Serum LPL mass assay

Lipoprotein lipase mass in preheparin serum was measured by the sandwich enzyme assay (ELISA) using a specific monoclonal antibody against bovine milk LPL, as described by Kobayashi et al. (16).

Urinary 8-OHdG analysis

Urine samples were centrifuged at 800 *g* for 10 min, and the supernatant was used for the determination of 8-hydroxy-2′-deoxyguanosine (8-OHdG) using a competitive enzyme-linked immunosorbent assay (8-hydroxy-2′-deoxyguanosine Check; Japan Institute for the Control of Aging, Shizuoka, Japan). The monoclonal antibody has been characterised and found to be specific for 8-OHdG (17). The result was expressed as per mg creatinine content (per mg Cr) in the same sample.

Statistical analysis

All data are expressed in mean ± SD STATVIEW ver. 4.51 (Abacus Concepts, Inc., Sakura-City, Chiba, Japan) for Macintosh was used for statistical processing. Student *t*-test was performed to determine whether the intergroup differences in levels were statistically significant at baseline and during study. Paired *t*-test was performed to determine whether the intragroup differences at baseline and 6 months

were statistically significant. The relationship between changes in CAVI, urinary 8-OHdG, serum LPL mass and other variables was analysed using stepwise multivariate and simple regression analysis. In all comparisons, values of $p < 0.05$ were considered statistically significant.

Results

Participant characteristics of two groups at baseline and after 6 months. The clinical profile of the subjects is shown in Table 1. The two groups did not differ significantly in any of the baseline parameters. After 6 months of treatment, CAVI significantly decreased only in glimepiride group ($9.4 \pm 1.4 \rightarrow 8.9 \pm 0.8$, $p < 0.05$), and FPG and HbA1c decreased significantly in both groups, whereas IRI increased significantly in both groups.

Changes in metabolic parameters after 6 months of glimepiride or glibenclamide administration

The changes in HbA1c, IRI, serum LPL mass and urinary 8-OHdG during this study are shown in Figure 1.

In both groups, HbA1c was lowered significantly after 6 months of glimepiride or glibenclamide administration, but no significant difference was observed between two groups (Figure 1A). The increase in basal IRI in glibenclamide group was threefold higher than that in glimepiride group ($p < 0.05$, Figure 1B).

Serum LPL mass level was slightly increased in glimepiride group and decreased in glibenclamide group. The change in serum LPL mass level tended to be different between two groups ($p = 0.096$, Figure 1C).

Urinary 8-OHdG level was decreased in glimepiride group and increased in glibenclamide group. The change in urinary 8-OHdG level was significantly different between two groups ($p = 0.009$, Figure 1D).

Changes in CAVI after 6 months of glimepiride or glibenclamide administration

The changes in CAVI during this study are shown in Figure 2.

In both groups, CAVI decreased after 6 months. The decrease in CAVI was greater in glimepiride group than in glibenclamide group (-0.50 ± 0.98 vs. -0.04 ± 0.57, $p = 0.048$).

Ordinal logistic regression model on changes of CAVI

Result of the stepwise multiple ordinal regression analysis for the relationship between changes in CAVI and various clinical parameters is summarised in Table 2. The change of urinary 8-OHdG was a significant independent predictor for the change of CAVI.

Table 1 Participant characteristics of two groups at baseline and after 6 months of treatment

	Glimepiride		Glibenclamide	
	Baseline	6 months	Baseline	6 months
n (Male/Female)	20 (16/4)		20 (14/6)	
Age (years)	59 ± 13	–	59 ± 13	–
BMI (kg/m^2)	24.3 ± 3.6	24.4 ± 3.1	24.7 ± 5.1	25.0 ± 5.6
Body weight (kg)	68 ± 12	68 ± 11	68 ± 21	67 ± 23
CAVI	9.4 ± 1.4	8.9 ± 0.8*	9.4 ± 1.2	9.4 ± 0.9
TC (mg/dl)	202 ± 29	185 ± 31	230 ± 58	223 ± 57
TG (mg/dl)	146 ± 88	161 ± 106	164 ± 79	164 ± 112
HDL-C (mg/dl)	48 ± 13	48 ± 11	55 ± 17	58 ± 19
LDL-C (mg/dl)	124 ± 24	105 ± 26*	142 ± 55	132 ± 49
FPG (mg/dl)	204 ± 58	149 ± 53**	214 ± 87	160 ± 61*
HbA1c (%)	8.3 ± 0.8	6.6 ± 0.5***	8.7 ± 1.2	7.0 ± 0.7***
IRI (μU/ml)	7.3 ± 4.0	11.2 ± 7.3*	7.5 ± 8.3	19.7 ± 30.1*
Serum LPL mass (ng/ml)	60.3 ± 23.9	62.4 ± 17.8	60.5 ± 28.9	53.1 ± 22.0
Urinary 8-OHdG (ng/ml-Cr)	8.6 ± 3.7	7.1 ± 2.0	8.1 ± 2.6	10.9 ± 4.3**

Data are presented as mean ± SD. BMI, body mass index; CAVI, cardio-ankle vascular index; TC, total cholesterol; TG, triglycerides; HDL-C, HDL-cholesterol LDL-C, LDL-cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; IRI, immuno-reactive insulin LPL mass, lipoprotein lipase mass, 8-OHdG, 8-hydroxydeoxiguanosine. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. baseline.

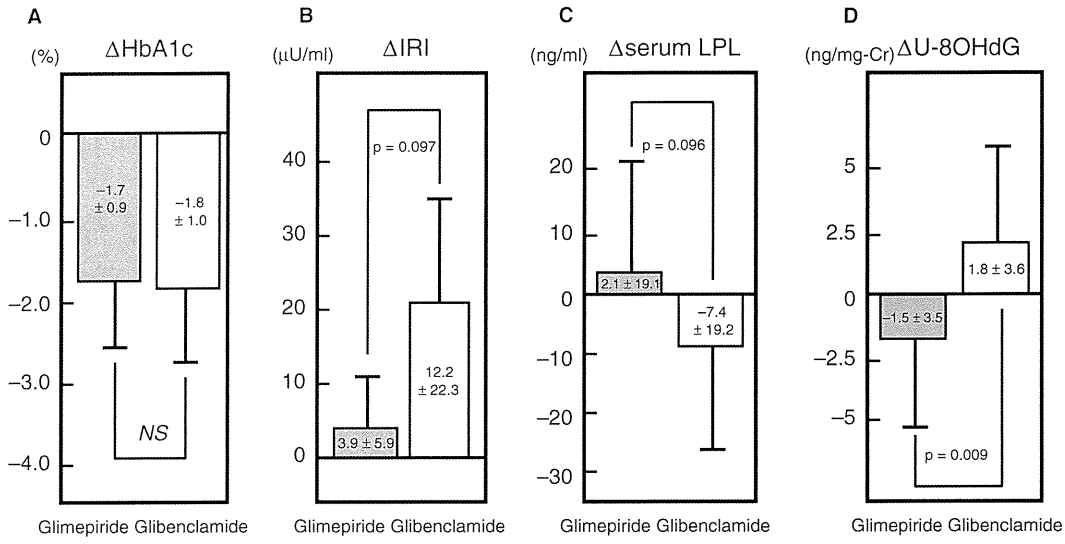

Figure 1 Changes in metabolic parameters after 6 months of glimepiride or glibenclamide treatment. Closed bar denotes glimepiride group, and open bar denotes glibenclamide group. Data are expressed as mean ± SD. Student's *t*-test was used in statistical analysis. HbA1c, glycosylated haemoglobin; IRI, immuno-reactive insulin; LPL, lipoprotein lipase; 8-OHdG, 8-hydroxydeoxiguanosine

Discussion

Unlike conventional SUs, glimepiride has been reported to have cardioprotective effect in subjects with acute coronary syndrome (18,19). However, the pleiotropic vascular effect of glimepiride has not been completely elucidated.

Cardio-ankle vascular index is generally high in patients with type 2 diabetes, but the mechanism remains unclear (20). Huang et al. (21) reported that hyperglycaemia was associated with increased CAVI in subjects without a clinical diagnosis of type 2 diabetes. Therefore, hyperglycaemia is considered to be an inducer of vascular dysfunction.

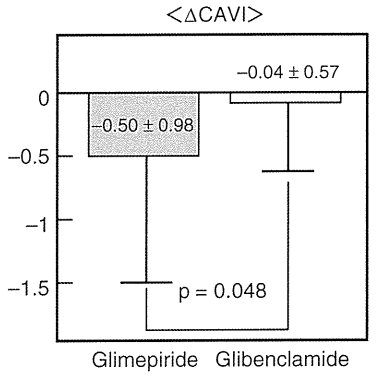

Figure 2 Changes in cardio-ankle vascular index (CAVI) after 6 months of glimepiride or glibenclamide treatment. Closed bar denotes glimepiride group, and open bar denotes glibenclamide group. Data are expressed as mean ± SD. Student's *t*-test was used in statistical analysis

In this study, no significant difference in change of HbA1c was found between the glimepiride and glibenclamide groups. However, the decrease of CAVI was greater in the glimepiride group than in the glibenclamide group. Nevertheless, the present results suggest that glimepiride may possess the unique effect of improving CAVI, which is independent of its hypoglycaemic action.

8-OHdG is a product of oxidative DNA damage following specific enzymatic cleavage after 8-hydroxylation of the guanosine base. Urinary 8-OHdG is a biomarker of the total *in vivo* systemic oxidative stress. Urinary 8-OHdG is also considered to be a biomarker of atherosclerosis (22,23) and macrovascular complications and is elevated in type 2 diabetes with hyperglycaemia (24–26). Oyama et al. (27) reported that the amount of 8-OHdG in culture medium was significantly higher when human umbilical vein endothelial cells (HUVECs) were cultured in high-glucose medium than when grown in normal-glucose medium. This finding suggests that high glucose-induced endothelial cell damages are mediated by augmented oxidative stress. Consequently, the hypoglycaemic effect conferred by glimepiride might contribute to the decrease of urinary 8-OHdG that indicates systemic oxidative stress. However, this phenomenon does not seem to be induced by the hypoglycaemic action, because a decrease of 8-OHdG was observed only with glimepiride and not with glibenclamide in spite of their equal hypoglycaemic effect. Glimepiride was also reported to upregulate eNOS activity and inhibit NF-κB activation in HUVECs (28). Therefore, glimepiride may have

Table 2 Correlation between change in cardio-ankle vascular index and various metabolic parameters analysed by ordinal logistic regression models

	Odds ratio	95% CI	*t*-value	p-value
Δ8-hydroxydeoxiguanosine (ng/mg-Cr)	0.28	0.06–0.49	3.02	0.019

The following variables were not accepted: Δ body weight, Δ fasting plasma glucose, Δ HbA1c, Δ immuno-reactive insulin, Δ triglycerides, Δ HDL-cholesterol, Δ LDL-cholesterol, and Δ serum lipoprotein lipase mass.

beneficial pleiotropic effect on vascular endotherial function by reducing endothelial oxidative stress as indicated by the decrease in urinary 8-OHdG. In this study, the change of urinary 8-OHdG was a significant independent predictor for the change of CAVI. These results might suggest that glimepiride improves arterial stiffness through reducing endothelial oxidative stress.

Several studies indicate that insulin resistance is associated with oxidative stress, and this association may result in vascular dysfunction and atherosclerotic diseases (3–5, 29). For example, NAD(P)H oxidase is known to be the most important source of reactive oxygen species (ROS) (23,30), and an increased amount of ROS produced via NAD(P)H oxidase activation has been demonstrated in the serum of patients with insulin resistance (4,31).

We have reported that serum LPL mass is a useful indicator of insulin resistance (1,32,33). Low serum LPL mass may reflect an increase in urinary 8-OHdG in subjects with insulin resistance. In the glimepiride group, urinary 8-OHdG was decreased, and serum LPL mass was increased after treatment. These results may suggest that glimepiride improves insulin resistance concerning with reducing systemic oxidative stress, and this mechanism may contribute to its beneficial pleiotropic vascular effect.

In summary, CAVI tended to decrease more markedly after 6 months treatment with glimepiride compared with glibenclamide. Furthermore, urinary 8-OHdG decreased and serum LPL mass increased after glimepiride treatment, and these changes were significant or tended to be significant compared with the changes after glibenclamide treatment. From these findings, we conclude that glimepiride improves arterial stiffness compared with glibenclamide. Furthermore, this effect of glimepiride may be induced not only by the hypoglycaemic action, but also by the reduction of oxidative stress associated with improved insulin resistance.

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Author contributions

Data analysis/interpretation, Statistics: Daiji Nagayama; Concept/design: Kohji Shirai; Critical revision of article: Yoh Miyashita, Atsuhito Saiki; Data collection: Kei Endo, Takashi Yamaguchi, Noriko Ban, Hidetoshi Kawana, Masahiro Ohira, Tomokazu Oyama.

References

1 Laakso M, Lehto S. Epidemiology of risk factors for cardiovascular disease in diabetes and impaired glucose tolerance. *Atheroclerosis* 1998; **137**: 65–73.
2 Woodfield S, Lundergan C, Reiner J et al. Angiographic findings and outcome in diabetic patients treated with thrombolytic therapy for acute myocardial infarction: the GUSTO-1 experience. *J Am Coll Cardiol* 1996; **28**: 1661–9.
3 Saiki A, Oyama T, Endo K et al. Preheparin serum lipoprotein lipase mass might be a biomarker of metabolic syndrome. *Diabetes Res Clin Pract* 2007; **76**: 93–101.
4 Furukawa S, Fujita T, Shimabukuro M et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest* 2004; **114**: 1752–61.
5 Fortuno A, Bidegain J, Jose GS et al. Insulin resistance determines phagocytic adenine dinucleotide phosphate oxidase overactivation in metabolic syndrome patients. *J Hypertens* 2009; **27**: 1420–30.
6 Rosskamp R, Wernicke-Pnten K, Draeger E. Clinical profile of the novel sulfonylurea glimepiride. *Diabetes Res Clin Pract* 1996; **31**: 33–42.
7 Draeger E, Wernicke-Panten K, Lomp HJ, Schuler E, Rosskamp R. Long-term treatment of type 2 diabetic patients with the new oral antidiabetic agent glimepiride. *Horm Metab Res* 1996; **28**: 419–25.
8 Scholzm GH, Schneider K, Knirsch W, Becker G. Efficacy and tolerability of glimepiride in daily practice. *Clin Drug Investig* 2001; **21**: 597–604.
9 Rosenstock J, Schneider J, Salmos E, Muscmore DB. Glimepiride, a new once-daily practice. *Diabetes Care* 1996; **19**: 1194–9.
10 Shakuto S, Sato Y, Ohshima K, Yaguchi M. Atheroprotective effects of a new sulfonylurea of the third generation, glimepiride. *J Diabet Complications* 2001; **15**: 68.
11 Shirai K, Utino J, Otsuka K, Tanaka M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). *J. Atheroscler. Thromb.* 2006; **13**: 1010–7.
12 Yambe T, Meng X, Hou X et al. Cardio-ankle vascular index (CAVI) for the monitoring of the atherosclerosis after heart transplantation. *Biomed Pharmacother* 2005; **59**: 177–9.

13 Kubozono T, Miyata M, Ueyama K et al. Clinical significance and reproducibility of new arterial distensibility index. *Circ J* 2007; **71**: 89–94.
14 Nakamura K, Tomaru T, Yamamura S, Miyashita Y, Shirai K, Noike H. Cardio-ankle vascular index is a candidate predictor of coronary atherosclerosis. *Circ J* 2008; **27**: 598–604.
15 Shirai K, Nema T, Hiroh Y, Itoh Y, Miyashita Y, Watanabe H. Clinical efficacy of the direct assay method using polymers for serum high density lipoprotein cholesterols. *J Clin Lab Anal* 1992; **11**: 82–6.
16 Kobayashi J, Hashimoto H, Fukamachi I et al. Lipoprotein lipase mass and activity in severe hypertriglyceridemia. *Clin Chem Acta* 1993; **216**: 113–23.
17 Toyokuni S, Tanaka T, Hattori Y et al. Quantitative immunohistochemical determination of 8-hydroxy-2′deoxyguanosine by a monoclonal antibody N45.1: its application to ferric nitrilotriacetate-induced renal carcinogenesis model. *Lab Invest* 1997; **76**: 365–74.
18 Klepzig H, Kober G, Matter C et al. Sulfonylureas and ischaemic preconditioning; a double-blind, placebo-controlled evaluation of glimepiride and glibenclamide. *Eur Heart J* 1999; **20**: 439–46.
19 Horimoto H, Nakai Y, Mieno S, Nomura Y, Nakahara K, Sasaki S. Oral hypoglycemic sulfonylurea glimepiride preserves the myoprotective effects of ischemic preconditioning. *J Surg Res* 2002; **15**: 181–8.
20 Ibata J, Sasaki H, Kakimoto T et al. Cardio-ankle vascular index measures arterial wall stiffness independent of blood pressure. *Diabetes Res Clin Pract* 2008; **870**: 265–70.
21 Huang CL, Chen MF, Jeng JS et al. Postchallenge hyperglycemic spike associate with arterial stiffness. *Int J Clin Pract* 2007; **61**: 397–402.
22 Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. *Clin Chim Acta* 2004; **339**: 1–9.
23 Hayaishi Okano R, Yamasaki Y, Kajimoto Y et al. Association of NAD(P)H oxidase p22 phox gene variation with advanced carotid atherosclerosis in Japanese type 2 diabetes. *Diabetes Care* 2003; **26**: 458–63.
24 Nishikawa T, Sasahara T, Kiritoshi S et al. Evaluation of urinary 8-hydroxydeoxyguanosine as a novel biomarker of macrovascular complications in type 2 diabetes. *Diabetes Care* 2003; **26**: 1507–12.
25 Negishi H, Ikeda K, Kuga S et al. The relation of oxidative DNA damage to hypertension and other cardiovascular risk factors in Tanzania. *J Hypertens* 2001; **19**: 529–33.
26 Endo K, Miyashita Y, Sasaki H et al. Probucol and atorvastatin decrease urinary 8-Hydroxy-2′-deoxyguanosine in patients with diabetes and hypercholesterolemia. *J Atheroscler Thromb* 2005; **13**: 68–75.
27 Oyama T, Miyashita Y, Watanabe H, Shirai K. The role of polyol pathway in high glucose-induced endotherial cell damages. *Diabetes Res Clin Pract* 2006; **73**: 227–34.
28 Jojima T, Suzuki K, Hirama N, Uchida K, Hattori Y. Glimepiride upregulates eNOS activity and inhibits cytokine-induced NF-κB activation through a phosphoinoside 3-kinase-Akt-depent pathway. *Diabetes Obes Metab* 2009; **11**: 143–9.
29 Delbosc S, Paizanis E, Magous R et al. Involvement of oxidative stress and NADPH oxidase activation in the development of cardiovascular complications in a model of insulin resistance, the fructose-fed rat. *Atherosclerosis* 2005; **179**: 43–9.
30 Mohazzab KM, Kaminski PM, Wolin MS. NADH oxidoreductase is a major source of superoxide anion in bovine coronary artery endothelium. *Am J Physiol* 1994; **266**: 2568–72.
31 Guzik TJ, Mussa S, Gastaldi D et al. Mechanisms of increased vascular superoxide production in human diabetes mellitus: role of NAD(P)H oxidase and endothelial nitric oxide synthase. *Circulation* 2002; **105**: 1656–62.
32 Watanabe H, Miyashita Y, Murano T, Hiroh Y, Itoh Y, Shirai K. Preheparin serum lipoprotein lipase mass level: the effects of age, gender, and types of hyperlipidemias. *Atherosclerosis* 1999; **145**: 45–50.
33 Shirai K, Itoh Y, Sasaki H et al. The effect of insulin sensitizer, troglitazone, on lipoprotein lipase mass in preheparin serum. *Diabetes Res Clin Pract* 1999; **46**: 35–41.

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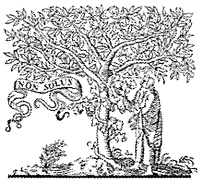

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Association between plate location and plate removal following facial fracture repair☆

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KEYWORDS
Facial fracture;
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Frontozygomatic suture

Summary *Background:* Titanium-based plates used to repair facial fractures are sometimes removed despite their high biocompatibility. Local discomfort can lead to plate removal surgery. Local discomfort may differ according to patient characteristics, tissue properties and plate thickness; however, little is known about the relationship between these conditions and plate removal.
Methods: We performed a hospital-based, retrospective cohort study of patients who underwent internal fixation for facial or frontal bone fracture. To identify factors associated with plate removal, we used multivariate logistic regression models.
Results: Data from 138 patients were analysed. All plates were made of commercially pure titanium, and all screws were made of titanium, 6% aluminium and 4% vanadium alloy. Plate thickness was 1.2 mm or 0.6 mm. Among plate locations, the frontozygomatic suture showed the highest percentage of complications (84%, 86 of 102 patients). The majority consisted of palpability and visibility. In patients who underwent plate removal ($n = 96$), all plates and screws were removed successfully. All plate-related complications were resolved after plate removal. No complications were introduced by plate removal. Plates 1.2 mm in thickness on the frontozygomatic suture had a relative risk of complications 2.48 times (95% confidence interval, 1.13–5.43) that of plates 0.6 mm in thickness. By multivariate analysis, the presence of plates on the frontozygomatic suture was a significant and independent risk factor for removal. Patients with plates on the frontozygomatic suture had a risk of plate removal 3.95 times (95% confidence interval, 1.55–10.07; $P < 0.01$) that of patients without plates on the frontozygomatic suture.

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Conclusion: Plates on the frontozygomatic suture have a high rate of complications. Thick plates increase these risks. Patients with plates on the frontozygomatic suture are more likely to undergo plate removal surgery than patients without plates on the frontozygomatic suture.

Introduction

Titanium-based plates and screws are commonly used for facial or frontal bone fracture repair.[1] The formerly used stainless steel or cobalt–chromium alloy can introduce a risk of malignant tumour formation, corrosion, metal toxicity, allergy and interference with X-ray imaging, computed tomography and magnetic resonance imaging.[2–5] Titanium and its alloy are thought to be free of these problems.[2,6] Commercially available titanium-based plates and screws for facial fracture repair usually consist of plates made of commercially pure titanium, and screws made of titanium, 6% aluminium and 4% vanadium (Ti–6Al–4 V) alloy.[2] The aluminium and vanadium increases hardness.[7] Titanium and its alloy have higher biocompatibility and corrosion resistance than stainless steel or cobalt–chromium alloy.[8,9]

In spite of their high biocompatibility, titanium-based plates and screws can cause complications and are sometimes removed.[10–13] Some clinical evidence suggests that local complication rates after internal fixation of facial fractures are similar for both titanium-based plates and stainless steel plates.[10,14–17]

We hypothesised that the potential for plate-related complications differs according to facial location, because the physical properties of facial tissues vary widely with location. In addition, plates used for facial fracture repair have a variety of thicknesses, and the thickness of the plates may affect the local complications. Moreover, patient characteristics vary widely. However, little is known about the association between these differences in conditions and complications.

Objective

To clarify the differences in complications by location and thickness of plates used for facial or frontal bone fracture and to determine the factors related to plate removal.

Design, setting

We performed a hospital-based, retrospective cohort study. The study protocol was approved by the ethical committee of Narita Red Cross Hospital. Written informed consent was not required.

Patients and methods

Selection of patients and study protocol

Patients aged 15 years or older who underwent internal fixation for frontal or facial bone fracture at the Narita Red Cross Hospital from September 2000 to October 2007 were identified retrospectively from the operative register.

Medical records were analysed retrospectively for data regarding sex, age at injury, cause of injury, medical comorbidity, type of anaesthesia, American Society of Anaesthesiologists (ASA) physical status category at the time of the internal fixation operation,[18] type of fracture, indication for plate placement, location, manufacturer, and composition of plates and screws, thickness of plates, the number of plates, prophylactic antibiotic, duration of antibiotic therapy, complications caused by plates during the follow-up period, retention or removal of plates and screws and complications after plate removal. The composition of the plates and screws and the thickness of the plates were determined from information available from their manufacturers.

Definitions of the ASA physical status categories are as follows.

PS 1: A normal healthy patient. No organic, physiologic or psychiatric disturbances.
PS 2: A patient with mild systemic disease. Controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease and mild obesity.
PS 3: A patient with severe systemic disease. Poorly controlled hypertension or diabetes, stable angina, previous heart attack, controlled congestive heart failure, bronchospastic disease with intermittent symptoms and morbid obesity.

Assignation of the ASA physical status was routinely performed before the general anaesthesia for the internal fixation operation by anaesthesiologists, of which at least one was a senior.

Statistical analysis

Continuous variables were compared with Student's *t*-test under the condition that equal variances could be assumed by Levene's test. Categorical variables were compared with Fisher's exact probability test. Relative risks and 95% confidence intervals were obtained. Multivariate logistic regression analyses were used to identify factors associated with plate removal. Adjusted odds ratios and 95% confidence intervals were obtained. Goodness of fit for the models was determined with the Hosmer–Lemeshow test. All *P* values quoted are two tailed. *P* values less than 0.05 were considered to indicate statistical significance. Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) software (version 13.0 J; SPSS, Chicago, IL, USA).

Results

A total of 138 patients met the criteria for the study. No absorbable osteosynthetic materials were used in the study period. All operations were undertaken by a single plastic surgical unit including one senior surgeon and three residents. Indications for plate placement were any displacement, any instability or possible instability by mastication. All internal fixation operations and all removal operations were performed under general anaesthesia. Co-morbidities of the patients were as follows: 28 patients were cigarette smokers, 15 patients had controlled hypertension, three patients had poorly controlled hypertension, six patients had diabetes, three patients had mild obesity, two patients had stable angina and one patient had previous heart attack. All patients received prophylactic antibiotic therapy. In all cases, one gram of cefazolin was administered intravenously just before starting the operation. After the operation, one gram of cefazolin was administered intravenously twice a day for 3 days.

All plates and screws were the products of Taguchi (Tokyo, Japan). All plates were made of commercially pure titanium and all screws were an alloy of titanium, 6% aluminium and 4% vanadium (Ti–6Al–4 V). Plates were 0.6 mm or 1.2 mm in thickness. Successful bone union was obtained in all cases.

During the study period, 345 titanium plates were place in 138 patients. The mean number of plates per patient was 2.5 plates (range: from two to 12 plates). The ranges of the number of plates by plate location were as follows: one to six on the frontal area, one to two on the nasal bridge, one on the frontozygomatic suture, one on the zygomaticomaxillary buttress, one on the piriform area, two on the mandibular angle, two to five on the mandibular body and two to three on the mandibular symphysis.

The types of the fracture patterns were as follows: four patients had a frontal bone fracture, seven patients had a naso-orbito-ethmoidal fracture, 99 patients had an orbito-zygomatic complex fracture, 41 patients had a maxillary fracture and 48 patients had a mandibular fracture.

Causes of injuries

Most fractures were caused by motor vehicle accidents. Fall was the second most common cause of injury. The number of patients by cause of injury was as follows: 82 (59%) patients were injured by motor vehicle accidents, 33 (24%) patients were injured in a fall, 12 (9%) patients were injured by blunt assault, 10 (7%) patients were injured in sports activity and two patients were injured by a horse kick. No fractures were caused by gunshot wounds. There were no pathological fractures.

Complications by locations

Complications with plates showed significant differences among plate locations (Figure. 1). The frontozygomatic suture showed the highest percentage of complications (84%, 86 of 102 patients). We performed a statistical comparison between the frontozygomatic suture and the infraorbital rim, because they are located near each other and both had relatively large sample sizes. The infraorbital rim showed a low percentage of complications (18%, 20 of 110 patients). Plates on the frontozygomatic suture had a relative risk of complications 4.64 times (95% confidence interval, 3.09–6.95; $P < 0.01$) that of plates on the infraorbital rim.

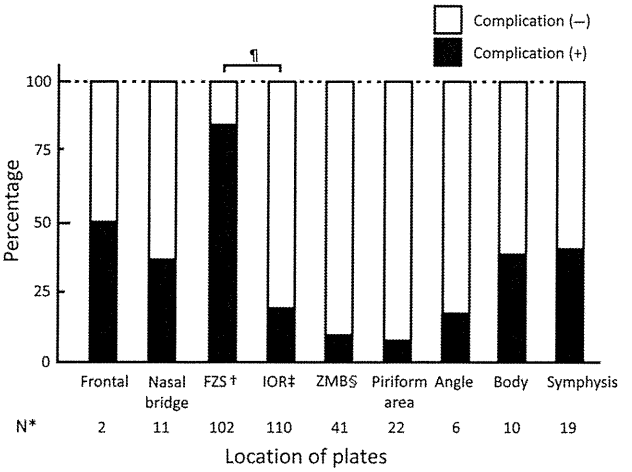

Figure. 1 Proportions of patients with complications by plate location: * The numbers of patients with plates by locations; † FZS denotes frontozygomatic suture; ‡ IOR denotes infraorbital rim § ZMB denotes zygomaticomaxillary buttress; ¶ Plates on the frontozygomatic suture have a relative risk of complications 4.64 times (95% confidence interval: 3.09–6.95; $P < 0.01$) that of plates on the infraorbital rim.

Palpability was the most frequently observed complication (Table 1). Visibility was the second most common complication. There were two cases of infection and one case of exposure.

Association between plate location and removal: univariate analyses

We performed statistical analyses to identify risk factors for plate removal by comparing patients who did not have their plates removed with those who had their plates removed. Removal of plates and screws was not done in 42 patients (retained group). The median follow-up period after internal fixation in the retained group was 382 days (range, from 310 to 701 days). Removal of plates and screws was performed in 96 patients (removed group). The median length of time between internal fixation and removal of plates in the removed group was 211 days (range, from 101 to 371 days). The median follow-up period after plate removal in the removed group was 257 days (range, from 184 to 402 days). In patients in the removed group, all plates and screws including both symptomatic and asymptomatic were removed simultaneously. All removal surgeries were performed with no major complications associated with the surgery itself or with the general anaesthesia. All plates and screws were removed successfully. In the removed group, all local complications related to the plates were resolved after plate removal. There were no local complications introduced by plate removal.

Table 1 Numbers of patients with complications by plate location.

Location	Infection	Exposure	Pain	Thermal hypersensitivity	Palpability	Visibility	Hypertrophic scar
Frontal	0	0	0	0	1	0	0
Nasal bridge	1	0	0	1	3	0	0
Frontozygomatic suture	0	0	2	7	69	15	1
Infraorbital rim	1	0	0	0	19	0	1
Zygomaticomaxillary buttress	0	1	1	1	1	0	0
Piriform area	0	0	0	0	2	0	0
Angle	0	0	0	0	1	0	0
Body	0	0	1	0	4	1	0
Symphysis	0	0	0	0	5	2	0

*Multiple answers are allowed.

There were no significant differences between the characteristics of the two patient groups (Table 2). In univariate analyses for the role of plate location, the frontozygomatic suture ($P = 0.02$), zygomaticomaxillary buttress ($P = 0.01$) and piriform area ($P = 0.01$) showed significant relationships with plate removal (Table 3).

Association between plate location and removal: multivariate analyses

We performed multivariate analyses using logistic regression models to adjust the associations between the explanatory variables for possible confounders. A multivariate analysis using a logistic regression model, where odds ratios were adjusted for age, sex, ASA physical status and the presence or absence of plates on every location showed that ASA physical status category (adjusted odds ratio, 0.23; 95% confidence interval, 0.10—0.58; $P < 0.01$) and the presence of the plates on the frontozygomatic suture (adjusted odds ratio, 33.31; 95% confidence interval, 3.48 to >99; $P < 0.01$) were significantly related to plate removal (Model 1 of Table 4). In the other model of multivariate logistic regression analysis, three locations that had shown significant relationships with plate removal in univariate analyses (Table 3: frontozygomatic suture, zygomaticomaxillary buttress and piriform area) were used (Model 2 of Table 4). Odds ratios were adjusted for age, sex, ASA physical status and the presence or absence of plates on these three locations. Model 2 also showed that a categorical increase in ASA physical status and the presence of plates on the frontozygomatic suture were significantly related to plate removal. The presence of plates on the frontozygomatic suture was an independent and significant risk factor for plate removal, and patients with plates on the frontozygomatic suture had a risk of plate removal 3.95 times (95% confidence interval, 1.55—10.07, $P < 0.01$) that of patients without plates on the frontozygomatic suture.

Table 2 Characteristics of the 138 patients in the study. Association with plate removal: univariate analyses.

Characteristics	Retained Group ($n = 42$)	Removed Group ($n = 96$)	*P* Value
Age (years)[a]	38 ± 17	36 ± 19	0.65
Sex (Number of Patients)			0.48
Female	6	20	
Male	36	76	
ASA PS (Number of Patients)[b]			0.19
PS 1	24	69	
PS 2	14	23	
PS 3	4	4	

PS 1 A normal healthy patient PS 2 A patient with mild systemic disease PS 3 A patient with severe systemic disease.

[a] Ages are presented as means ± SD. Student's t-test was used to compare the means of the two groups because equal variances could be assumed by Levene's test ($P = 0.33$).

[b] American Society of Anaesthesiologists Physical Status.

Effect of plate thickness

All plates used in the study period were made of commercially pure titanium and all screws were an alloy of titanium, 6% aluminium and 4% vanadium (Ti—6Al—4 V). Plates were 0.6 mm or 1.2 mm in thickness. Whether 0.6-mm or

Table 3 Association between plate location and removal surgery: univariate analyses.

Location (number of patients with plates)	Retained Group ($n = 42$)	Removed Group ($n = 96$)	*P* Value
Frontal	0	2	1.00
Nasal bridge	5	6	0.31
Frontozygomatic suture	25	77	0.02
Infraorbital rim	32	78	0.50
Zygomaticomaxillary buttress	18	19	0.01
Piriform area	12	10	0.01
Mandibular angle	0	6	0.18
Mandibular body	6	4	0.07
Mandibular symphysis	5	14	0.80

Table 4 Factors associated with plate removal: multivariate analyses.

Explanatory variable	Adjusted odds ratio	95% CI[b]	*P* value
Model 1[a]			
Age per 10 years increase	1.18	0.87–1.60	0.30
Male sex	4.38	1.18–16.22	0.27
A categorical increase in ASA PS[c]	0.23	0.10–0.58	<0.01
Frontal	>99	0.00 to >99	1.00
Nasal bridge	2.80	0.39–20.43	0.31
Frontozygomatic suture	33.31	3.48 to >99	<0.01
Infraorbital rim	0.12	0.01–1.73	0.12
Zygomaticomaxillary buttress	0.46	0.13–1.57	0.22
Piriform area	0.73	0.15–3.51	0.69
Mandibular angle	>99	0.00 to >99	1.00
Mandibular body	0.12	0.01–1.78	0.12
Mandibular symphysis	2.70	0.38–18.96	0.32
Model 2[a]			
Age per 10 years increase	1.05	0.80–1.36	0.74
Male sex	2.60	0.84–8.08	0.10
A categorical increase in ASA PS[c]	0.38	0.17–0.83	0.02
Frontozygomatic suture	3.95	1.55–10.07	<0.01
Zygomaticomaxillary buttress	0.43	0.14–1.37	0.15
Piriform area	0.67	0.17–2.68	0.57

[a] Odds ratios were adjusted for age, sex, ASA PS, and presence or absence of plates on all locations listed in the table. To evaluate trends in odds, ASA PS (ordinal variable) was modelled as single, continuous, independent variable. There was no evidence of lack of fit for the model in the Hosmer–Lemeshow goodness of fit test.
[b] CI denotes confidence interval.
[c] ASA PS denotes American Society of Anaesthesiologists Physical Status.

1.2-mm plates should be used was decided on a case-by-case basis depending on the surgeons' preferences and opinions.

There was a significant relationship between plate thickness and complication in the frontozygomatic suture. Plates 1.2 mm in thickness on the frontozygomatic suture had a relative risk of complications 2.48 times (95% confidence interval, 1.13–5.43; $P < 0.01$) that of plates 0.6 mm in thickness. Ninety-one patients had a 1.2-mm-thick plate fixed over their frontozygomatic suture. Among these 91 patients, 82 patients had complications related to plates on their frontozygomatic suture. Meanwhile, 11 patients had a 0.6-mm-thick plate fixed on frontozygomatic suture. Among these 11 patients, four patients had complications related to plates on the frontozygomatic suture.

In the analysis of the association between plate thickness and removal at the frontozygomatic suture, although the proportion of patients who underwent plate removal was higher for patients with plates of 1.2 mm in thickness than for those having plates 0.6 mm in thickness, it was not statistically significant (relative risk, 1.43; 95% confidence interval, 0.83–2.48; $P = 0.13$). Among 91 patients who had a 1.2-mm-thick plate fixed on their frontozygomatic suture, 71 patients had an operation to remove it. Meanwhile, among 11 patients who had a 0.6-mm-thick plate on frontozygomatic suture, six patients had a removal operation.

Discussion

The main causes of injury in our study were similar to those in other reports: motor vehicle accident, fall and blunt assault.[14,16,19–21] Unlike in other reports, none of our patients had injuries caused by gunshot wounds.[14,16,22] This might be the result of the very strict gun control in Japan.

Rates of complications caused by plates varied widely by plate location in our study. Plates on the frontozygomatic area had a tendency to cause more complaints than those on other areas, as in other studies.[13,15,23] Although the frontozygomatic suture and infraorbital rim are located near each other and are often fixed simultaneously in facial fracture repair, such as with zygomatic fractures, there was a significant difference in discomfort caused by plates at these locations. The difference in discomfort might be caused by differences in anatomical properties between the frontozygomatic area and the infraorbital area.[24,25] Because thin skin lies over the prominent bones, a plate on the frontozygomatic suture can be prone to palpability, bulging appearance, thermohypersensitivity and pain.

The presence of plates on the frontozygomatic suture was a significant and independent risk factor for plate removal in our study. Patients who had plates on the frontozygomatic suture were about four times more likely to undergo removal surgery. We suggest that the discomfort related to the plates

on the frontozygomatic suture might lead patients to undergo removal surgery and that the thickness of the plates on frontozygomatic suture is one of the factors linked to the high proportion of patients with discomfort on the frontozygomatic suture. Thus, the presence of plates on the frontozygomatic suture is a significant risk factor for plate removal.

Thicker plates on the frontozygomatic suture were related to more discomfort than were thinner plates in our study. Based on our study and other reports, the frontozygomatic suture is one of the most uncomfortable areas after internal fixation. Palpability was the most common complication related to a plate on the frontozygomatic suture in our study. Meanwhile, palpability is not regarded as a common adverse event in other reports. Measurements of palpability are prone to be subjective. Palpability revealed only by meticulous palpation or palpability without discomfort was not regarded as complication in our study. The use of thin plates is an option to reduce the discomfort caused by plates on the frontozygomatic suture, although there is controversy regarding their fixation strength.[11,26] Although it is difficult to conclude definite causality between plate thickness and complications because of the small sample size and observational nature of our study, currently, we always use a thin titanium plate on the frontozygomatic suture. We believe thin titanium plates can be beneficial for the rest of the upper facial area because the cortical bones there are thin. We do not believe that very rigid fixation strength is required for the upper face. For the mandible, we believe thick plates are better because of their fixation strength.

We had no patients in whom absorbable plates and screws were used in the study period. We believe that absorbable plates and screws are useful for paediatric craniofacial surgery patients. We also believe the fixation strength of absorbable plates and screws are sufficient for achieving bone union of fracture of the upper face in adults. However, for frontozygomatic suture, we prefer not to use absorbable plates and screws because of their thickness and the inflammation accompanying biodegradation.[27] Absorbable plates available in Japan have a thickness of 0.9, 1.0 and 1.4 mm. All of them are thicker than the thinnest titanium plate of 0.6 mm. It takes several years for absorbable plates to be degraded mainly by hydrolysis *in vivo*. Degradation is achieved not only by hydrolysis but also by inflammation. We think it undesirable that there is inflammation in thin skin over the frontozygomatic suture because it can lead to exposure or discomfort.

The overall rate of plate removal was 70% (96 of 138 patients) in our study. Three patients underwent plate removal surgery because of infection or exposure. It is difficult to compare these results with other reports, because plate removal policies vary.[13–17,23,28–30] We have a treatment principle that non-absorbable plates and screws used for facial or frontal bone fracture repair should be removed electively after serving their clinical functions. For plate removal, we usually remove all plates and screws. Unlike other countries, such as the United States, a considerable number of hospitals in Japan have a policy of elective complete removal. This difference in removal policy may result from a difference in perceived risks from foreign materials and a difference in medical care systems between countries.[7,8,31]

The rate of infection and exposure was 2% (three of 138 patients). Others have reported a per-patient infection and exposure rate of 3–9% after internal fixation of facial fractures under symptomatic removal intention.[15,17,23,32] Although it is difficult to make a simple comparison between our results and those of others, we think that the relatively low infection and exposure rate in our study is partially the result of our elective removal principle that can avoid preventable complications after bone healing. Islamoglu et al. reported that all infections were seen after bone union.[13] O'Connell et al. reported the lowest per-patient infection and exposure rate of 3% (15 of 535 patients) under a symptomatic removal policy.[32] We agree that careful preoperative, intraoperative and postoperative managements as indicated in their report are essential for preventing infection and exposure.

Complications related to the presence of plates were diminished after plate removal in all patients who underwent removal surgery. There were no complications introduced by plate removal. The removal of non-functioning plates did not appear to cause undue risk to patients in our study.

Patients with a higher category of ASA physical status were significantly more unlikely to undergo removal surgery. We suggest that reluctance to undergo more surgery with general anaesthesia is associated with hesitation about plate removal.

The observational nature of our study makes it difficult to infer causality. The generalisability of our data is unknown because the study was conducted at only one hospital.

Conclusions

Plates on the frontozygomatic suture cause high rates of complications. The presence of plates on the frontozygomatic suture is a significant and independent risk factor for plate removal after facial or frontal bone fractures. Thick plates on the frontozygomatic suture are associated with significantly higher rates of complications than thin ones. The use of thin plates is a possible choice for reducing complications related to plates on the frontozygomatic suture.

Conflict of interest

None.

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References

1. Soejima K, Sakurai H, Nozaki M, et al. Semi-closed reduction of tripod fractures of zygoma under intraoperative assessment using ultrasonography. *J Plast Reconstr Aesthet Surg* 2009;**62**: 499–505.
2. Haug RH. Retention of asymptomatic bone plates used for orthognathic surgery and facial fractures. *J Oral Maxillofac Surg* 1996;**54**:611–7.
3. Jackson IT, Adham MN. Metallic plate stabilisation of bone grafts in craniofacial surgery. *Br J Plast Surg* 1986;**39**:341–4.
4. von Domarus H. Stabilisation of the mandible by A.O. compression plate after mandibulotomy. *Br J Plast Surg* 1981; **34**:389–91.
5. Woodman JL, Black J, Nunamaker DM. Release of cobalt and nickel from a new total finger joint prosthesis made of vitallium. *J Biomed Mater Res* 1983;**17**:655–68.
6. Blake GB, MacFarlane MR, Hinton JW. Titanium in reconstructive surgery of the skull and face. *Br J Plast Surg* 1990;**43**: 528–35.
7. Merritt K, Margevicius RW, Brown SA. Storage and elimination of titanium, aluminum, and vanadium salts, in vivo. *J Biomed Mater Res* 1992;**26**:1503–15.
8. Woodman JL, Jacobs JJ, Galante JO, Urban RM. Metal ion release from titanium-based prosthetic segmental replacements of long bones in baboons: a long-term study. *J Orthop Res* 1984;**1**:421–30.
9. Manor Y, Chaushu G, Taicher S. Risk factors contributing to symptomatic plate removal in orthognathic surgery patients. *J Oral Maxillofac Surg* 1999;**57**:679–82.
10. Alpert B, Seligson D. Removal of asymptomatic bone plates used for orthognathic surgery and facial fractures. *J Oral Maxillofac Surg* 1996;**54**:618–21.
11. Kuvat SV, Cizmeci O, Bicer A, et al. Improving bony stability in maxillofacial surgery: use of osteogenetic materials in patients with profound (> or =5mm) maxillary advancement, a clinical study. *J Plast Reconstr Aesthet Surg* 2009;**62**:639–45.
12. Malata CM, McLean NR, Alvi R, et al. An evaluation of the Wurzburg titanium miniplate osteosynthesis system for mandibular fixation. *Br J Plast Surg* 1997;**50**:26–32.
13. Islamoglu K, Coskunfirat OK, Tetik G, Ozgentas HE. Complications and removal rates of miniplates and screws used for maxillofacial fractures. *Ann Plast Surg* 2002;**48**:265–8.
14. Chaushu G, Manor Y, Shoshani Y, Taicher S. Risk factors contributing to symptomatic plate removal in maxillofacial trauma patients. *Plast Reconstr Surg* 2000;**105**:521–5.
15. Francel TJ, Birely BC, Ringelman PR, Manson PN. The fate of plates and screws after facial fracture reconstruction. *Plast Reconstr Surg* 1992;**90**:568–73.
16. Murthy AS, Lehman Jr JA. Symptomatic plate removal in maxillofacial trauma: a review of 76 cases. *Ann Plast Surg* 2005;**55**:603–7.
17. Stone IE, Dodson TB, Bays RA. Risk factors for infection following operative treatment of mandibular fractures: a multivariate analysis. *Plast Reconstr Surg* 1993;**91**:64–8.
18. Mak PH, Campbell RC, Irwin MG, American Society of A. The ASA physical status classification: inter-observer consistency. American Society of Anesthesiologists. *Anaesth Intensive Care* 2002;**30**:633–40.
19. Lim LH, Lam LK, Moore MH, Trott JA, David DJ. Associated injuries in facial fractures: review of 839 patients. *Br J Plast Surg* 1993;**46**:635–8.
20. Back CP, McLean NR, Anderson PJ, David DJ. The conservative management of facial fractures: indications and outcomes. *J Plast Reconstr Aesthet Surg* 2007;**60**:146–51.
21. MacKinnon CA, David DJ, Cooter RD. Blindness and severe visual impairment in facial fractures: an 11 year review. *Br J Plast Surg* 2002;**55**:1–7.
22. Nguyen V, Wollstein R. Civilian gunshot wounds to the fingers treated with primary bone grafting. *J Plast Reconstr Aesthet Surg* 2009;**62**:e551–5.
23. Nagase DY, Courtemanche DJ, Peters DA. Plate removal in traumatic facial fractures: 13-year practice review. *Ann Plast Surg* 2005;**55**:608–11.
24. Lee JW. Treatment of enophthalmos using corrective osteotomy with concomitant cartilage–graft implantation. *J Plast Reconstr Aesthet Surg* 2010;**63**:42–53.
25. Chen CT, Lai JP, Chen YR, et al. Application of endoscope in zygomatic fracture repair. *Br J Plast Surg* 2000;**53**:100–5.
26. Kim MG, Kim BK, Park JL, et al. The use of bioabsorbable plate fixation for nasal fractures under local anaesthesia through open lacerations. *J Plast Reconstr Aesthet Surg* 2008;**61**:696–9.
27. Xia Z, Triffitt JT. A review on macrophage responses to biomaterials. *Biomed Mater* 2006;**1**:R1–9.
28. Brown JS, Trotter M, Cliffe J, Ward-Booth RP, Williams ED. The fate of miniplates in facial trauma and orthognathic surgery: a retrospective study. *Br J Oral Maxillofac Surg* 1989;**27**: 306–15.
29. Iizuka T, Lindqvist C, Hallikainen D, Paukku P. Infection after rigid internal fixation of mandibular fractures: a clinical and radiologic study. *J Oral Maxillofac Surg* 1991;**49**:585–93.
30. Moreno JC, Fernandez A, Ortiz JA, Montalvo JJ. Complication rates associated with different treatments for mandibular fractures. *J Oral Maxillofac Surg* 2000;**58**:273–80. discussion p. 80–1.
31. Assem FL, Levy LS. A review of current toxicological concerns on vanadium pentoxide and other vanadium compounds: gaps in knowledge and directions for future research. *J Toxicol Environ Health B Crit Rev* 2009;**12**:289–306.
32. O'Connell J, Murphy C, Ikeagwuani O, Adley C, Kearns G. The fate of titanium miniplates and screws used in maxillofacial surgery: a 10 year retrospective study. *Int J Oral Maxillofac Surg* 2009;**38**:731–5.