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Diseases

Highlights

- Diabetic Nephropathy
- Plasma Uric Acid Levels
- The Oncology Scenario
- Connective Tissue Diseases

Discovering Thoughts, Inventing Future

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Diseases

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The Oncology Scenario in India: Lots of Gaps Need to be Bridged

By Dr. Virender Suhag, Dr. Sunita Bs, Dr. Ak Singh, Dr. Sunita Dashottar,
Dr. Manoj Semwal, Dr. Sukhvir Singh & Dr. Nishant Lohia

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Abstract- As the second most populous nation and one of the fastest-growing major economies, India faces many challenges, one such burning issue is the provision of cancer care. There is a huge gap in the demand and supply of health care resources in Indian oncology scenario, mainly due to steadily aging populations and also to current trends in smoking prevalence and the growing adoption of unhealthy lifestyles. Slightly more than 1 million new cases of cancer are diagnosed every year in a population of 1.2 billion. Although incidence of cancer is low in India compared with high-income countries, mortality is high; with approximately 600,000- 700,000 deaths in 2012. Many cancer cases in India are associated with tobacco use, infections, and other avoidable causes. Cancer can have profound psychological, social and economic consequences for people in India, often leading to family impoverishment and societal inequity. Currently, overall public expenditure on health care is only 1.5% of GDP. The socioeconomic, service delivery and cost and resource implications from this enormous burden require urgent attention from central and state governments, cancer communities, and public health communities to reduce their effect in a sustainable and cost-effective manner.

Keywords: cancer, india, challenges, recommendations.

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The Oncology Scenario in India: Lots of Gaps Need to be Bridged

Dr. Virender Suhag [α], Dr. Sunita Bs [σ], Dr. Ak Singh [ρ], Dr. Sunita Dashottar [ω], Dr. Manoj Semwal [¥], Dr. Sukhvir Singh [§] & Dr. Nishant Lohia [χ]

Abstract- As the second most populous nation and one of the fastest-growing major economies, India faces many challenges, one such burning issue is the provision of cancer care. There is a huge gap in the demand and supply of health care resources in Indian oncology scenario, mainly due to steadily aging populations and also to current trends in smoking prevalence and the growing adoption of unhealthy lifestyles. Slightly more than 1 million new cases of cancer are diagnosed every year in a population of 1.2 billion. Although incidence of cancer is low in India compared with high-income countries, mortality is high; with approximately 600,000-700,000 deaths in 2012. Many cancer cases in India are associated with tobacco use, infections, and other avoidable causes. Cancer can have profound psychological, social and economic consequences for people in India, often leading to family impoverishment and societal inequity. Currently, overall public expenditure on health care is only 1.5% of GDP. The socioeconomic, service delivery and cost and resource implications from this enormous burden require urgent attention from central and state governments, cancer communities, and public health communities to reduce their effect in a sustainable and cost-effective manner. We discuss specific barriers that must be overcome to improve prevention and early detection, enhance prompt treatment, and provide cost-effective palliative care for patients with advanced stage disease.

Keywords: cancer, india, challenges, recommendations.

I. Introduction

Population growth, ageing and life style changes are the largest contributors to the increasing total number of cancer cases and the shift in the burden of cancer and other chronic diseases in economically developing countries.1,2 With 1 million new cases and 683 000 deaths estimated in 2012 by GLOBOCAN, and 1.7 million new cases and 1.2 million deaths projected to occur in 2035, cancer is a major public health challenge in India.3-5 At any given point, an estimated 2.5 million people live with a previous diagnosis of cancer. Although the age-standardized rate of cancer is 92.4 per 100 000 men and 97.4 per 100 000 women, the age-adjusted incidence for all types of cancer in India in urban areas ranges from 92.1 to 126.1 per 100 000 for men and from 107.8 to 142.0 per 100 000 for women. Although overall cancer incidence is lower in India than in most high-income countries, the relative mortality rates are higher.6-8.

More than 30% of these cancers are preventable, mainly by not using tobacco, having a healthy diet, being physically active and moderating the use of alcohol.9 There is a need for commitment for tackling cancer by reducing risk factors and strengthening the existing screening and treatment facilities. Social factors, especially inequalities, are major determinants of India's cancer burden, with poorer people more likely to die from cancer before the age of 70 years than those who are more affluent. Most of the Indian population does not have access to a well organized and well regulated cancer care system. Failure to address social inequalities reduces survival and can needlessly increase the costs of cancer to individuals and Indian society as a whole.10-12 Strategies are urgently needed to formulate treatment policies that are not merely based on international guidelines from high-income countries, but are tailored to specific settings in India. Rebalancing of the distribution of power, social goods, and resources will be a crucial determinant of how India will address its cancer burden in the long term.12,13

II. Dismal Public Funding

The delivery of affordable and equitable cancer care is one of India's greatest public health challenges. Public expenditure on cancer in India remains below US$10 per person (compared with more than US$100 per person in high-income countries), and overall public expenditure on health care is still only slightly above 1% of gross domestic product. Out-of-pocket payments, which account for more than three-quarters of cancer expenditures in India, are one of the greatest threats to patients and families, and a cancer diagnosis is increasingly responsible for catastrophic expenditures that negatively affect not only the patient but also the welfare and education of several generations of their family.6, 10,14 No other comparable nation spends as small a proportion of its national resources on public health care. Government of India should consider a variety of financing and delivery options to universalize health care services. The cost of universal health care delivered through a combination of public and private providers is estimated to be INR 1713 per capita per year in India.15 Given that the poorest two-thirds of the

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population is in much greater need of better health-care provision than is the wealthiest third, increased public investment in health services needs to be a public policy priority for India. 12 The only way to fight this scourge under such circumstances is to have pragmatic programmes and policies based on currently available scientific information and sound public health principles.16 Some states in India have rolled out social insurance programs that provide free tertiary care to households below the poverty line, the replication of such success across the country has not been realized.10,17

III. Lacunae in Cancer Registries

Cancer registration is the process of continuing, systematic collection of data on the occurrence and characteristics of reportable neoplasms with the purpose of helping to assess and control the impact of malignancies on the community; and can be either population based (PBCR) or Hospital based cancer registry (HBCR).18 Due to lack of uniform reporting and under capture of data, the actual burden of cancer in India is much greater than reflected through the existing literature and hence can be regarded as a 'tip of iceberg' situation. The distribution of population based cancer registries is grossly uneven with certain important parts of the country being not represented at all and hence the current cancer burden is not reflected by registry data. Projection of load of cancer mortality helps in quantifying the burden of cancer and is essential for planning cancer control activities. There have not been many attempts to project the cancer mortality burden at the country level in India mainly due to lack of data on cancer mortality at the national and state level. It is recommended that all oncology centers and multispecialty hospitals maintain their hospital based cancer registries and collate the data with the state and national registries.9,19,20 Analysis of the routine data on cancers in a cancer registry remains an essential component in understanding the epidemiology of cancers in limited resources setting.21 Hospital-based registries are important tools for policy formulations and region-specific data creation.[22]

IV. Lack of Radiotherapy Centres

About 85% of the world's people live in developing countries including India, but these countries house only about one third of the world's radiotherapy facilities. At least 50% to 60% of cancer victims in the developing world can benefit from radiotherapy, but most developing countries do not have enough radiotherapy machines or sufficient numbers of specialized doctors and other health professionals. Establishing hospital networks and streamlining of referral services can improve cancer care in our country.23,24 There is great diversity in the existing Radiotherapy facilities in corporate hospitals of metropolitan cities on one hand; and the government hospitals and state-funded medical colleges on the other hand. Most corporate hospitals are equipped with the state-of-art latest linear accelerators compatible with highest form of conformal radiotherapy; including intensity modulated radiotherapy, image guided radiotherapy and stereotactic body radiotherapy. Most government run tertiary- care hospitals impart radiotherapy by primitive telecobalt complexes and conventional linear accelerators. This diversity is mainly due to financial constraints, lack of enough resources, faulty planning and inadequate management.24 All efforts must be made to upgrade the infrastructure and existing facilities in state-run tertiary care hospitals. Brachytherapy can play a very important role in the definitive cure by radiation therapy in India. However, except for in a handful of centers, the majority of hospitals use it only for intracavitary treatment. The most probable reasons for the same are the lack of logistical resources in terms of trained personal and supporting staff, rather than lack of radiotherapy machines and equipment.25

V. Tobacco: The Giant Killer

Tobacco is the single largest cause of preventable death among adults globally, as it is in India. Despite this alarming situation, there is very minimal inclusion of tobacco in formal education systems, including the medical discipline. It can be concluded that tobacco control is not receiving adequate attention in public health curricula in India. There is a need for coordinated efforts in the area of tobacco control so as to reduce morbidity and mortality from tobacco induced diseases.26 Results from recent surveys show that 274.9 million Indians (35% of the total adult population, plus 14.1% of school children aged 13–15 years) are tobacco users, mainly in the form of smokeless tobacco. Overall, tobacco-related disease is estimated to kill 2.8 million Indians annually.6 The ban on the manufacture, sale and use of gutka and pan masala in some states of India is a big stride in prevention process of tobacco-related oral and oropharyngeal cancer.24 Public welfare organizations in India and the media have to come together to pursue the campaign against tobacco, combined with programmes of education and awareness, early detection and screening, has to be taken up. However, implementation of tobacco control directives has been hampered by pressure from the tobacco industry, irregular taxation of tobacco products, cultural issues, and low exposure to antitobacco information without delay. Efforts should be made to increase the awareness of The Cigarettes and Other Tobacco Products Act (COTPA) focusing on younger population, less educated, and those belonging to the low SES.27

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There is a need of capacity building initiatives to equip physicians with skills in tobacco cessation.[28]

VI. Insurance Schemes

Nearly two-thirds of Indian households seek healthcare from the private medical sector due to dismal public health scenario mainly on account of continuous neglect, worker absenteeism, long wait times, shortages of supplies, and absence of diagnostic facilities. Access to oncological care is becoming increasingly difficult for the underprivileged. Despite the emergence of a number of health insurance programmes and schemes, only 5% of households report that a household member has coverage of any kind. One admission to hospital can consume a sizeable share of a poor household's resources, commonly leading to financial crisis. Private for-profit insurers target the better-off section of the society with expensive packages but have little to offer to Indian's poor. More attention should be paid to the innovative indigenous health insurance schemes that are helping to address the weakness in health care financing and provision. Insurance is a welcome necessary step and must doubtless expand to help in facilitating equitable health care to shift to sections for which government is responsible. Indeed for those not able to access insurance it is government that will have to continue to provide the minimum services, and intervene against market failures including denial through adverse selection or moral hazard. Community based insurance, where members of a community, linked by geographical proximity or through employment-based relationships such as local trade unions, pool resources to share the financial risk of ill health, can play some role in this scenario.[24,29]

VII. Long Waiting Period

In India patients have to wait for a longer time before active treatment of cancer is started. This may be due to various factors like confirmation of diagnosis, arrangement of finance, seeking expert's opinion, getting date for surgery etc. If left untreated cancer continues to grow. The rate of growth can be variable but it is known to be high in many epithelial malignancies.24,30 Investigations of O' Rourke and Edwards (2000) have shown that 21 percent of potential curable lung cancer patients became incurable while waiting for treatment.31 In this circumstances 'Telemedicine' services can be of great help. Regional Cancer Centers (RCC) must develop a web-based telemedicine system, linking various cancer centers of the state. Patients can take the help of the doctors at the local teleclinic and access specialist service at RCC for consultation and follow-up. It is much cheaper to set up telemedicine centers in smaller town than to open super specialty hospital in large cities. [24]

VIII. Lack of Palliative Care

At present, out of one million newly diagnosed Indian cancer patients each year, more than 50 % will die within 12 months of diagnosis and another one million cancer survivors (within 5 years of diagnosis) will show progressive disease. Out of these 1.5 million in need of palliative care (PC) less than 0.1 million patients can be covered by the existing facilities. Unfortunately, majority of patients in India present with late-stage disease and have limited access to palliative care and effective pain-relieving medications, such as morphine. It is recommended that the existing Oncology centers should include PC services with trained 'doctor nurse team'. For India, outpatient palliative care clinics will render meaningful and cost-effective practice. Thereafter, the medical institutions and NGOs can expand the service to integrate 'homecare' within a locality or region. Cancer pain relief still remains the cornerstone of optimal palliative care. Complementary and alternative medicines may play some role in selected cases in providing some help to these patients for treatment and palliation.24,32 Key barriers related to pain management include the role of nursing, opioid misperceptions, bureaucratic hurdles, sociocultural/ infrastructure challenges, limited national palliative care policy and lack of institutional interest in palliative care. Interventions should be undertaken to streamline process of morphine procurement, work within the existing sociocultural infrastructure to ensure opioids reach patients most in need, target unexpected audiences for symptom management education, and account for role expectations of health care providers.33 Systematic and continuous education for medical staff is mandatory, and a major break-through for achieving this purpose would be to increase the number of courses and faculties in palliative medicine at most universities.[34]

IX. Inadequate Screening and Vaccination Programmes

Widespread uptake of human papilloma virus (HPV) vaccine could reduce incidence and mortality by two-thirds in India, which bears the greatest burden of the disease with 132,000 cases and 74,000 deaths yearly.35 Common barriers for HPV acceptability among parents include concerns about side effects, vaccine cost, and missing work to receive the vaccine. Addressing parental concerns, health worker training and polices, and efforts to minimize cost will be central to successful HPV vaccine implementation.36 Unfortunately, ill-informed anti-HPV-vaccine campaigns and media and political frenzies have substantially undermined the prospects of introduction of HPV vaccination, which could substantially reduce morbidity, mortality, and health-care costs in the country in which a fifth of the global cases of cervical cancer occur. In view

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of the challenges to introduce cervical screening programmes and given the level of development of health services in several states, introduction of HPV vaccination for girls aged 9–13 years in the national immunisation programme should be a high priority, since the individuals who cannot afford vaccination need it the most. At the core of any cancer control strategy, the essential components should include cost-effective interventions for the following components: tobacco control, infection control, healthy eating, a curable cancer program and palliative care.[3,24]

X. Scarcity of Health Workers in India

India, which has a total population of 1.25 billion, has only 1500 trained oncologists. The cancer patient-to-oncologist ratio in India is an abysmal 1600:1, compared to an estimated 100:1 in USA. It is understandable that oncologists in India have to shoulder a heavy clinical burden, leaving a little time for clinical research.37 It often leads to delay in diagnosis and instituting definitive management, thereby compromising the oncological outcome. The unequal distribution of these workers poses an even more substantial issue. Several factors explain the paucity of trained health workers in rural areas, including disinclination of physicians to work and live in low socioeconomic areas; lack of funding from the public sector to adequately staff rural facilities and provide necessary equipment; reluctance of junior medical officers to work in an isolated working environment with low salaries and inadequate supervision and training; and few private health-care institutions in rural areas where salaries are often less lucrative. Overcoming medical workforce shortages, particularly in oncology, will need efforts to reduce international emigration and strategies that can increase distribution of staff to rural areas.[6]

XI. Sociocultural Barriers and Gender Inequality

Major sociocultural issues that affect approaches to health care in India include social taboos, castes, gender inequality, low regard for health as a priority, nihilistic approaches to cancer diagnosis, blind faith in traditional methods of healing, religious dynamics, and widespread superstitions. Although these factors are more prevalent in rural India, they also exist in urban areas. Social taboos frequently prevent individuals from seeking conventional health-care assessments, and subsequently lead to advanced stages of disease by the time a trained doctor is seen, particularly for socially stigmatized diseases such as cancer. Patients can often keep a diagnosis of cancer secret, and go to extreme lengths to conceal a cancer diagnosis from family and friends, even at the cost of compromising treatment and outcomes. Gender inequality exists in many parts of India, which results in neglect of many female health problems. Notwithstanding some changes in attitude towards the role of women in Indian society, the country remains patriarchal, with men having power and authority both in the community and in the family. Last, but not least, faith in traditional and alternative forms of medicine is widespread among the Indian public. These medicine men frequently rely on chants, rituals, worships and sacred powders to cure patients with disease. Strong faith in these healers prevents establishment of modern scientific medicine in more remote rural areas in India.[6,38]

XII. Recommendations and Conclusion

- New multidisciplinary oncology centers based on public-private partnership must be established in middle-tier cities, suburban and rural areas to ensure homogenous distribution of comprehensive state-of-art facilities throughout India.
- There is a need to develop cost-effective and low-maintenance indigenous Telecobalt units and Linear accelerators which can be commissioned in rural and suburban areas
- Medical Council of India and National Board of Examinations, the governing bodies which regulate post graduate teaching, must add more seats in Oncology and allied specialties; and must ensure an all-inclusive curriculum suitable for Indian scenario
- Revision of curriculum of undergraduate and post graduate programs of medical, nursing and para-medical fraternity to familiarize them with basic principles of oncology so that they can provide evidence-based primitive care at their own levels before referral to nearby regional cancer centers.
- Addition of palliative care beds in various oncology centers and training community health workers to provide bed side palliative care.
- Extensive persuasive health education to be directed towards control / reduce the tobacco habit. National and international efforts to strengthen to make childhood vaccination against HBV and HPV universally available and affordable overcoming the economic and political barriers.
- People at all levels should be educated to change their behavior to avoid preventable cancers. Public awareness in nutrition education, safe sexual practice, attention to personal and genital hygiene needs.
- Development of innovative approaches most suited to Indian populations to design protocols which are simple, affordable and safe.
- Establishment of research groups, development of a reliable clinical databases, tumor banks, and simple clinical protocols, in addition to research to identify biomarkers for diagnosis.

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- India needs to adopt immediately the concept of "nurse practitioners" who have been trained to take a call on treatment in the absence of a qualified doctor and training the rural health workers in cancer treatment so that once a patient has undergone radiotherapy and chemotherapy at a bigger centre, care in the later phase can happen at respective homes.

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Effects of Bosentan on the Skin Temperature of Hands and Feet in Patients with Connective Tissue Diseases Complicated with Raynaud's Phenomenon: A Prospective, Open-Label, Uncontrolled, Single-Center Study

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Abstract- Objective: To assess the effects of bosentan on Raynaud's phemonenon and the skin temperature of hands and feet in patients with connective tissue diseases (CTDs) complicated with digital ulcers or pulmonary arterial hypertension (PAH).

Methods: An open-label, non-controlled, single-center, prospective study, which was designed to exclude the seasonal bias. Bosentan was commenced from 62.5mg twice daily for four to six weeks, followed by 125mg twice daily for 10 to 12 weeks (total period was 16 weeks). Bosentan was reduced or discontinued if adverse events were appearing. Patients without adverse events for 16 weeks continued the trial for 52 weeks.

Keywords: digital ulcers, endothelin receptor antagonist, pulmonary arterial hypertension, secondary Raynaud's phenomenon, systemic sclerosis, thermography.

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Results: In 13 enrolled patients, six were patients with suspected PAH and eight had digital ulcers. Ten patients were diagnosed with systemic sclerosis (eight with limited cutaneous and two with diffuse cutaneous form), two with mixed connective tissue disease and one with systemic sclerosis (diffuse cutaneous form)-polymyositis overlap syndrome.

After 16-week bosentan therapy, the frequency and the duration of Raynaud's phenomenon was significantly decreased (P=0.009, P = 0.008, respectively). Not the numbness, but the cold sensation of hands and feet was also improved (P = 0.021). Skin temperature measured by thermography was not increased after 16-week treatment, but the significant increases were seen after 52 weeks, respectively (P = 0.038 & P = 0.025). Nasal bleeding in one patient and liver dysfunction in four patients was investigated.

Coclusions: It was suggested that the long-term treatment of bosentan could improve the decreased skin temperature in CTD patients with secondary Raynaud's phenomenon.

Keywords: digital ulcers, endothelin receptor antagonist, pulmonary arterial hypertension, secondary Raynaud's phenomenon, systemic sclerosis, thermography.

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I. Introduction

Endothelins are consisted with 21-amino acid and induce potent vasoconstriction (1). There are three isoforms in endothelins (ET1-3) and their receptors are divided into ETA, ETB1, ETB2 and ETC. Bosentan is an antagonist of ETA and ETB and is clinically indicated for pulmonary arterial hypertension (PAH) and ongoing digital ulcers (2). PAH is one of serious complications in some connective tissue diseases (CTDs), such as mixed connective tissue disease (MCTD), systemic sclerosis (SSc) and systemic lupus erythematosus, and influences to their prognosis (3).

On the other hand, Raynaud's phemonenon is another symptom in CTDs that is not commonly critical, but often impairs quality of life and may lead occasionally digital ulcers. Raynaud's phemonenon is induced by cold temperature or emotional stress. It gets worse in winter, and is diminished since the end of winter and usually disappears during the summer. To judge the effectiveness of medicines for Raynaud's phemonenon, the timing to evaluate is very important. For example, it is not fair to estimate the efficacy in spring or summer for the therapy starting from midwinter. However the point to evaluate Raynaud's phemonenon has not been clear in most of the reports (4-11). Herein, to exclude the seasonal bias, we set observation time strictly and investigated the efficacy of bosentan on Raynaud's phemonenon and the skin temperaturein patients with CTDs.

II. Materials and Methods

a) Study design

The probe was planned as an open-label, non-controlled, single-center, prospective study. Patients were recruited from the outpatient clinic of the Department of Rheumatology and Applied Immunology, the Saitama Medical University Hospital. Bosentan was

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commenced since the end of November, from 62.5mg twice daily for four to six weeks, followed by 125mg twice daily for 10 to 12 weeks (total period was 16 weeks). Bosentan was reduced or discontinued if adverse events were appearing. Patients without adverse events for 16 weeks continued the trial for 52 weeks. Prior medications administered for more than 12 weeks were permitted to continue (Table 1).

Table 1 : Patient background

No.	Disease	Gender	Age (years)	Disease Duration (years)	PAH (WHO FC)	No. of DU or DUS	Prior Medication
1	lcSSc	F	77	21	0	2U, 1S	Beraprost Sarpogrelate
2	lcSSc	F	76	17	III	0	Sarpogrelate
3	lcSSc	F	71	25	II	0	Beraprost
4	lcSSc	F	71	15	0	1U	Beraprost
5	lcSSc	F	65	16	II	0	Beraprost Sarpogrelate
6	lcSSc	F	62	1	0	6S	Beraprost
7	lcSSc	F	53	18	0	2U, 1S	Beraprost Sarpogrelate
8	lcSSc	M	53	1	II	0	NA
9	dcSSc	M	71	16	III	1S	Beraprost Sarpogrelate
10	dcSSc	F	45	11	0	2U	Sarpogrelate
11	lcSSc PM	F	59	24	0	1U, 1S	Beraprost Sarpogrelate
12	MCTD	F	58	11	II	0	NA
13	MCTD	F	45	7	0	1U	Beraprost Sarpogrelate

The study protocol conformed to the principles of the Declaration of Helsinki and was approved by the institutional review board of the Saitama Medical University Hospital (09-028-1).

b) Patients

Patients with SSc (12) and systemic lupus erythematosus (SLE) (13) were diagnosed according to the American College of Rheumatology criteria, MCTD according to the criteria proposed by the Special Research Committee for MCTD of the Japanese Ministry of Health and Welfare (Kasukawa criteria) (14) and polymyositis (PM) according to the Bohan and Peter's criteria(15). PAH was suspected from more than four out of six clinical and laboratory findings, including exertional dyspnea, systolic pulsation on the left sternum, increase of the pulmonary segment of the second cardiac sound, enlargement of the base of the pulmonary artery or protrusion of the left second aortic arch in the chest X-ray, right ventricular hypertrophy or load as diagnosed by the electrocardiogram, right ventricular enlargement, right ventricular load or right ventricular pressure greater than 35 mmHg by the Doppler echocardiogram. Patients with ischemic heart diseases, valvular diseases unrelated with PAH and congenital heart diseases were excluded.

c) Clinical evaluation

Raynaud's phemonenon was evaluated by the diaries as follows; the number of the attacks daily, the duration of the attacks daily and an assessment of severity of cold sensation and numbness of hands and feet by a visual analogue scale (VAS) of 100 mm. The number of digital ulcers and scars were recorded at the baseline, at Week 16 and at Week 52, or at the time of dropped-out. Thermography was carried out just before starting bosentan, after 16 weeks and after 52 weeks receiving bosentan. After sitting on the chair for 20 min in the room at 26°C, 50 ± 10% humidified, the skin temperature of hands and feet was measured by the thermography (Nihon Kohden, Tokyo, Japan). We compared the mean temperature of twelve points on the regions between the back side of interphalangeal joints and the base of thumbnails, between the back side of distal interphalangeal joints and the base of the other fingernails, between the back side of interphalangeal joints and the base of first toenails, between the back side of distal interphalangeal joints and the base of the other toenails and on the center of the back of hands and feet before and after the administration of bosentan (Fig 3a, b).

d) Statistical anlysis

Wilcoxon's signed rank test was used for comparisons between paired data. P values of less than 0.05 were considered significant. Statistical analyses were performed using IBM SPSS statistics software version 18.0 (IBM SPSS Japan, Tokyo, Japan).

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III. Results

a) Patients

Three patients were recruited in 2009, five in 2010, two in 2011 and three in 2012. Enrolled in this study were 13 patients, of which half a dozen patients had suspected PAH (four; NYHA functional class II and two; class III) and eight had digital ulcers. No one underwent right heart catheterization. Ten patients were diagnosed with SSc (eight with limited cutaneous and two with diffuse cutaneous form), two with MCTD and one with SSc (diffuse cutaneous form)-PM overlap syndrome. The patient background was summarized in Table 1. Raynaud's phenomenon was present in all patients and ten patients were accompanied with nail fold bleeding. Bosentan was discontinued in one patient due to nasal bleeding at Week 6. Since liver dysfunction appeared at the dosage of 250mg bosentan in four patients, the dosage was decreased to 125mg. Of those patients, two discontinued at Week 16 and two continued for 52 weeks. Eight patients could be increased to 250mg of bosentan, of which, one patient transferred to the nearby clinic after week 16 and seven continued for 52 weeks.

b) Raynaud's phenomenon

After 16-week treatment with bosentan, the frequency and the duration of Raynaud's phenomenon were significantly decreased ($P=0.009$ and $P = 0.008$, respectively, Fig. 1a, b); both frequency and duration of Raynaud's phenomenon improved in nine patients and only the duration improved in one patient. Two patients did not experience any changes. Not the numbness, but the cold sensation with VAS was also significantly improved (Fig. 1c,d). After the treatment of 52-week administration of bosentan, the frequency and the duration of Raynaud's phenomenon were significantly decreased as well (data not shown).

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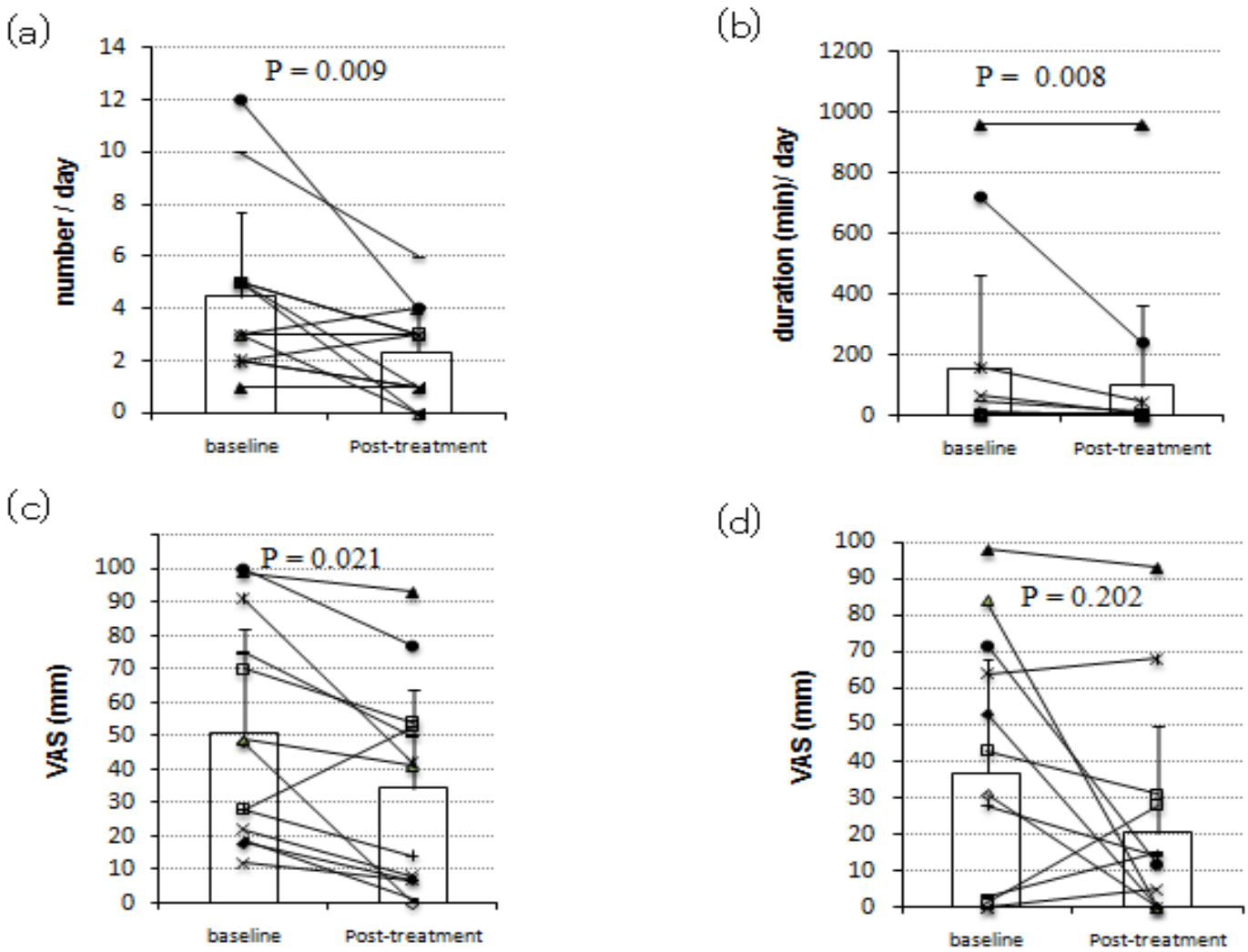

Figure1 : Effect of bosentan treatment on Raynaud' s phenomenon after 16-week treatment
One patient was dropped out at week six. Open columns and error bars mean average and standard deviation (n=12)
(a) the daily frequency of Raynaud's phenomenon, (b) the daily duration of Raynaud's phenomenon, (c) severity of the cold sensation of hands and feet by visual analogue scale (VAS), (d) severity of numbness of hands and feet by VAS.

c) Digital ulcers

Digital ulcers of all patients became scarred or disappeared after bosentan administration. Namely, nine digital ulcers improved to six scars in seven patients and ten digital ulcer scars decreased to six in five patients after the treatment for 16 weeks. New digital ulcers were not recognised throughout the treatment.

d) Thermography

The skin temperature of ten patients were monitored by thermography at Week 16 and nine patients at Week 52. No significant increase of the skin temperature was detected at Week 16, but the significant increase was seen at Week 52, respectively (Fig. 2, P = 0.038 & P = 0.025). Representative results were shown in Fig. 3c and d.

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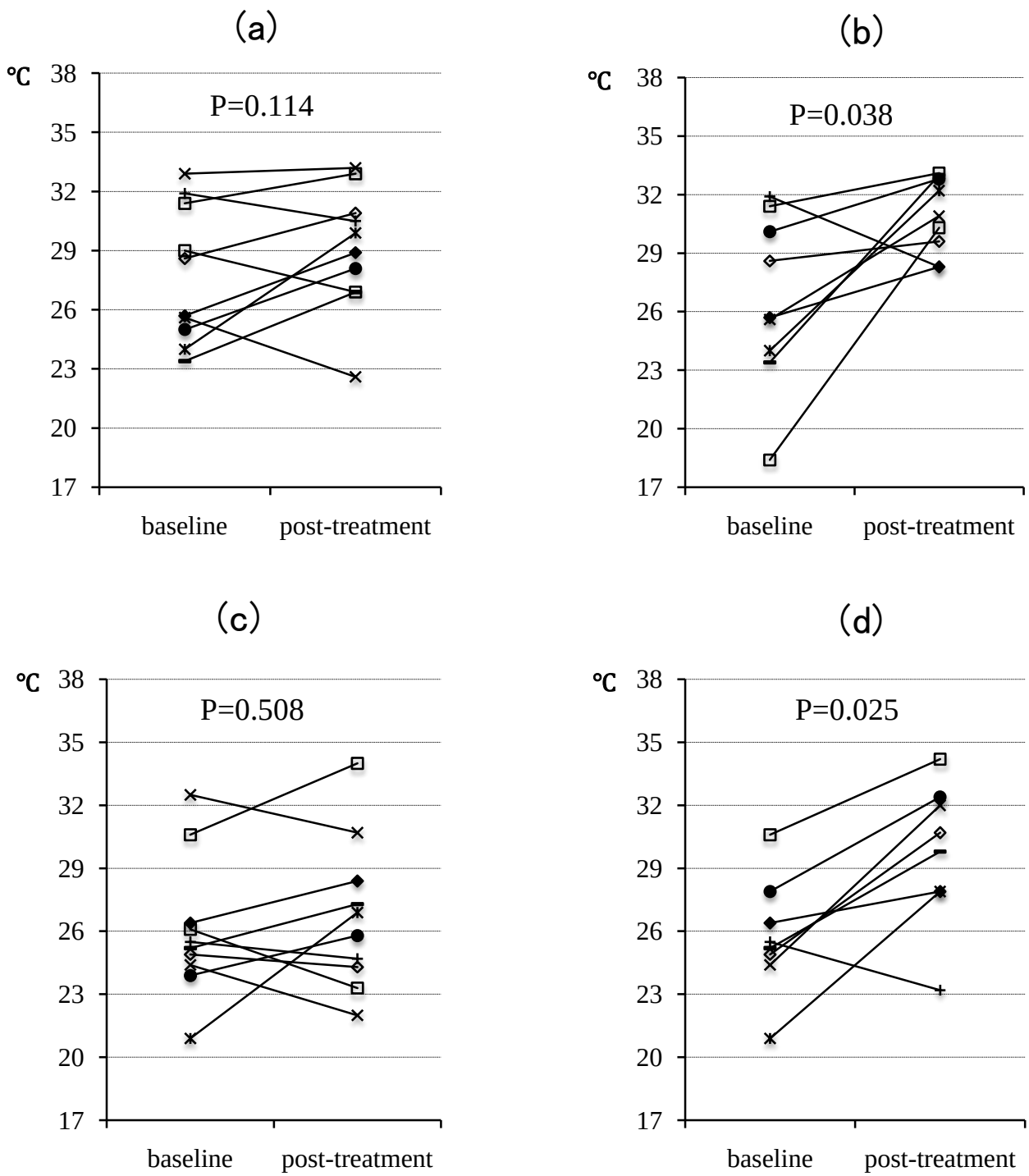

Figure 2 : The skin temperature of hands and feet measured by thermography before and after bosentan treatment. Hands (a) and feet (c) before and after the 16 week treatment (n=10), hands (b) and feet (d) before and after the 52 week treatment (n=9).

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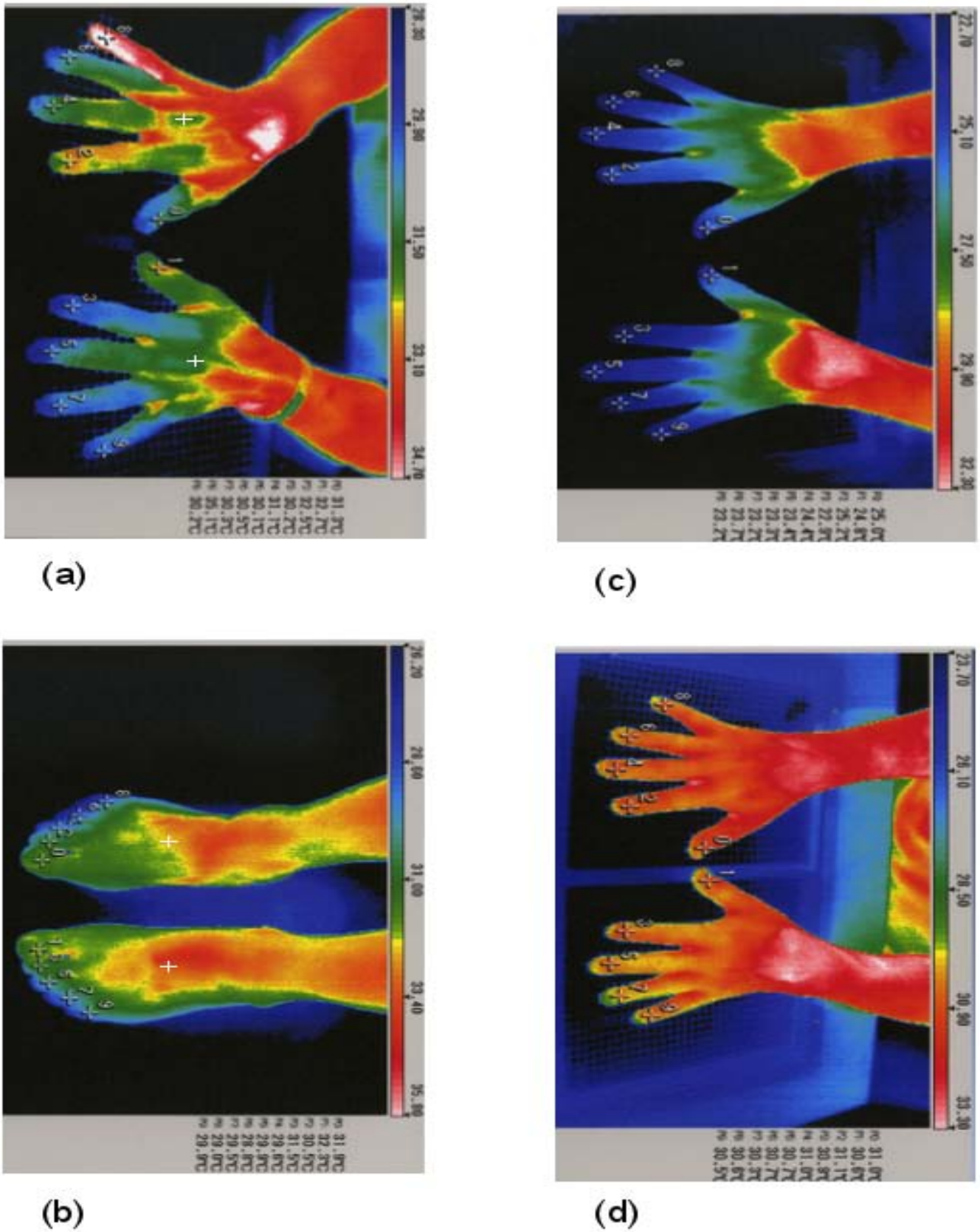

Figure 3: Thermography findings The skin temperature of twelve points in hands (a) and feet (b) was checked out by thermography. Representative thermographic pictures of the good responder (case 8) at week 0 (c) and week 52 (d).

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IV. Discussion

Concerning the remedy for Raynaud's phenomenon, calcium channel blockers (CCBs) (16), oral prostacyclin analogues (4), or serotonin receptor antagonists (17, 18) have been prescribed. As CCBs lower blood pressure strongly, patients with hypotension cannot be administered them sufficiently. The effect of latter two agents is almost insufficient as well. ET participates in not only pulmonary circulation, but also peripheral circulation. Accordingly, the ET-receptor antagonist, bosentan has an anti-PAH effect, but also is expected to have an improving effect of peripheral circulatory disturbance. In fact, many researchers reported that bosentan was subjectively effective for Raynaud's phenomenon (5-7, 19, 20), oppositely, others did that the medicine was ineffetive (8-10). These reports were shown in table 2.

Table 2 : Comparison between literatures and the present study

Study	Design	Disease: patient number	Entry time	Evaluation time	Subjective effect	Objective effect	Remarks
Ramos-Casals et al.[19]	Case report	dcSSc: 1, lcSSc: 3	Unknown; 1, January; 2, December;1	Unknown: 1, May: 3	Effective	NT	None
Funauchi et al.[6]	Single center, retrospective	dcSSc: 7, lcSSc: 6, MCTD: 2	Unknown, various	Various	Effective	NT	None
Hettema et al.[5]	Single center, prospective	lcSSc: 15	Unknown	Week 8, 16	Effective	Not improved by photoelectric plethysmography	The outdoor temperature was higher at Week16 than baseline.
Giordano et al.[7]	Single center, retrospective	dcSSc: 4, lcSSc: 10	Unknown	Week 4, 12, 24, 48	Effective at Week 12, 24, 48, not at Week4	Effective by videocapillaroscopy at Week 48	None
Selenko-Gebauer et al.[20]	Single center, retrospective	lcSSc: 1, MCTD: 1, pre-SSc: 1	November	Week 16 (March)	Effective	Effective by thermography	None
The present study	Single center, prospective	dcSSc: 2, lcSSc: 8, dcSSc-PM: 1, MCTD: 2	End of November	Week 16, 52	Effective	Effective by thermography at Week52, not at Week16	None
Rosato et al.[9]	Single center, open-label, prospective	Bosentan (PAH+): dcSSc: 14, lcSSc: 16, nifedipine (PAH-): dcSSc: 15, lcSSc: 15	Winter?	Week 4, 8, 16	Ineffective	Effective by laser doppler perfusion imaging at Week 8 and 16, not at Week4, ineffective by videocapillaroscopy	None
Moore et al.[10]	Single center, prospective	dcSSc: 6, lcSSc : 12	Unknown,	Week 24	Ineffective	Ineffective by videocapillaroscopy at Week24	None
Nguyen et al.[8]	Single center, randomized, prospective, double-blind	Bos: dcSSc: 3, lcSSc: 6, placebo: dcSSc: 1, lcSSc: 7	Winter	Week 16	Ineffective	NT	DcSSc was more in the bosentan group than placebo. Effectivity of the placebo group (57%) was fairly high.

Bos: bosentan; dc SSc: diffuse cutaneous systemic sclerosis; lc SSc: limited cutaneous systemic sclerosis; MCTD: mixed connective disease; NT: not tested; PAH: pulmonary arterial hypertension; PM: polymyositis

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As mentioned above, the timing of the evaluation is very important to judge restrictly the effectiveness of treatments for Raynaud's phemonenon. For example, one of patients was estimated the efficacy in May in Ramos-Casals and co-workers' report (19), and Hettema et al. (5) reported the improvement of Raynaud's phemonenon at Week 8 and Week 16, but the outdoor temperature was significantly higher at Week 16, it was thought that seasonal improvement might be appended to their final results. Funauchi et al. (6) reported that Raynaud's phenomenon improved somewhat in 13 out of 15 patients with a median of eight weeks of treatment and that Raynaud's phenomenon disappeared in eight of them after a median of 14 weeks. They did not indicate when bosentan had initiated. Giordano et al. (7) reported 14 patients decreased in daily numbers and daily duration of Raynaud's phemonenon at 12 weeks, 24 weeks and 48 weeks, but not at four weeks after the administration of bosentan. They did not indicate when bosentan had initiated either. Therefore the improvement at 24 weeks must be influenced with seasonal recovery and the result at 12 weeks was not clear either. In contrast to these, Nguyen et al. reported that bosentan did not improve the frequency, duration, pain or severity of Raynaud's phemonenon after 16-week treatment as compared with placebo (8). The trial was the only one double-blinded test of bosentan for Raynaud's phenomenon. It is superior to other reports in the point which was able to exclude the placebo-effect. But the protocol permitted participants to start from anytime in winter. Starting examination from the latter of winter, considerable participants could bring spontaneous improvement after 16 weeks. Actually, because even the placebo group showed 57% reduction of the daily frequency of Raynaud's phemonenon attacks after 16 weeks, not a few patients might be affected by not only placebo effect but also a seasonal improvement. In other double-blinded studies (16,21), the examination period was six or seven weeks and the improvement rates of placebo groups were much lower. On the other hand, Selenko-Gebauer et al. (20) were initiated bosentan in November and evaluated the outcome after 16 weeks, it seemed that the evaluation points were fairly strict. Their cases were improved, however the participants were only three. We also started bosentan from the end of November and estimated the effectiveness at the end of March, in which the temperature is same as that in November at Saitama where our hospital located, and investigated the significant improvement. Although placebo effects could not be excluded, the present study suggested that bosentan was effective to Raynaud's phenomenon.

Bosentan has been evaluated the objective effectiveness for peripheral circulation. Selenko-Gebauer et al. (20) reported that the temperature of hands by the thermography increased after 16-week treatment, but the result was only three analyses including one patient of pre-scleroderma. Rosato et al. (9) reported that bosentan improved the blood flow of fingers by a Lisca laser Doppler perfusion imager after eight- and 16-week treatment. Hettema et al. reported that the blood flow determined by photoelectric plethysmography during cooling and rewarming did not improve after 16-week treatment (5). Giordano et al. reported that visibility and sludging of nailfold by the videocapillaroscopy improved after 48-week treatment (7). Moore et al. reported that 24-week administration showed no improvement of nail fold capillary density and dimensions by the videocapillaroscopy either (10). Our data showed no significant improvement of skin temperature by the thermography after 16-week treatment, but 52-week treatment demonstrated the significant increase. Generalizing the present findings and the other reports, it was thought that bosentan needs the long-term use to improve peripheral circulatory disturbance significantly.

Although bosentan has been indicated for the prevention of new digital ulcers, a long-term use of bosentan might not be recommended for Raynaud's phenomenon alone from a viewpoint of medical economy because the prognosis of Raynaud's phenomenon is generally much better than that of digital ulcers or PAH. When we focus on the medicines except conventional drugs or bosentan, it was reported that the efficacy of phosphodiesterase-5 (PDE-5) inhibitors is equal to or more than bosentan as for the treatment of Raynaud's phenomenon (21, 22). PDE-5 inhibitors might be more practicable because they are more inexpensive than bosentan. As for ERAs except bosentan, ambricentan blocks selectively the binding of endothelin-1 to ETA which induces vasoconstriction.It was reported that ambricentan decreased the number of Raynaud's phenomenon and healed digital ulcers in patients with SSc who had failed bosentan (11). Macitentan blocks both ETA and ETB as well as bosentan. The former is a non-competitive antagonist and inhibits ETA strongly compared to ETB, while the latter is a competitive antagonist. Additionally, it was reported that macitentan suppresses the proliferation of sclerodermic fibroblasts (23). These reports indicate that it is worth evaluating the efficacy of new ERAs released after bosentan on the peripheral circulatory disturbance including Raynaud's phenomenon.

In conclusion, the present study suggested that long-term use is required to pull out the full potential of bosentan on peripheral circulatory disturbance in CTDs.

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Diabetic Nephropathy: Causative and Protective Factors

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Keywords: diabetic nephropathy, causative factor, protective factor, protein kinase c, connective tissue growth factor, nuclear factor kappa b, osteopontin, reactive oxygen species, netrin-1, adiponectin.

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DIABETICNEPHROPATHYCAUSATIVEANDPROTECTIVEFACTORS

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Diabetic Nephropathy: Causative and Protective Factors

Guanjing Zhang[α], Liang Zhou[σ], Zhiyan Xu[ρ], Khrystyna Pronyuk[Ѡ], Xingming Chen[¥] & Hairong Wang[§]

Abstract- Diabetic nephropathy (DN) is the major cause of chronic kidney disease (CKD) which normally leads to end stage renal disease (ESRD) or dialysis. Despite vigorous management including treatment of hypertension, glyceamic control and the utilization of inhibitors of renin angiotensin system (RAS), a significant proportion of diabetic patients still develop CKD and progress to ESRD. Advances in understanding of the pathogenesis and pathology of DN have made it clear that DN occurs as a result of imbalance between causative factors and endogenous protective factors. To emphasize this concept, this review will focus on some of the current knowledge concerning both causative and endogenous protective factors of DN.

Keywords: diabetic nephropathy, causative factor, protective factor, protein kinase c, connective tissue growth factor, nuclear factor kappa b, osteopontin, reactive oxygen species, netrin-1, adiponectin.

I. Introduction

Diabetic nephropathy (DN), a common and severe complication of Diabetes mellitus (DM), is the major cause of chronic kidney disease (CKD) which normally leads to end stage renal disease or dialysis. It is estimated that the number of people with diabetes will double by 2030 around the world, and the situation is more serious in developing country [1, 2]. The mortality of dialysis patients with DN is higher than that of non-diabetic patient [3]. Thus, the thorough understanding of pathophysiology of DN will be one of the most important medical concerns in the future.

Numerous efforts have been made to investigate the molecular mechanism of DN with an aim to identify causative factors. The data indicated that hemodynamic and metabolic factors contribute to the development of DN [4-6]. Hemodynamic factors include alterations in flow and pressure, and the activation of renin-angiotensin system (RAS) [3]. Hyperglycemia related pathways are also activated, which lead to the formation of advanced glycation end products (AGEs), over-expression of protein kinase C (PKC), increased oxidative stress [5, 6]. Clinical strategies based on some of these causative factors for preventing DN, include inhibition of RAS via angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB); endothelin antagonists [7, 8]. However, recent studies demonstrate that these clinical strategies only delay but cannot stop the progression of DN [9, 10].

Advances in understanding of the pathogenesis and pathology of DN have made it clear that DN occurs as a result of imbalance between causative factors and endogenous protective factors (Fig. 1). Both aspects of DN mechanisms provide potential targets for disease prevention. To emphasize this concept, this review will focus on some of the current knowledge concerning both causative factors and endogenous protective factors.

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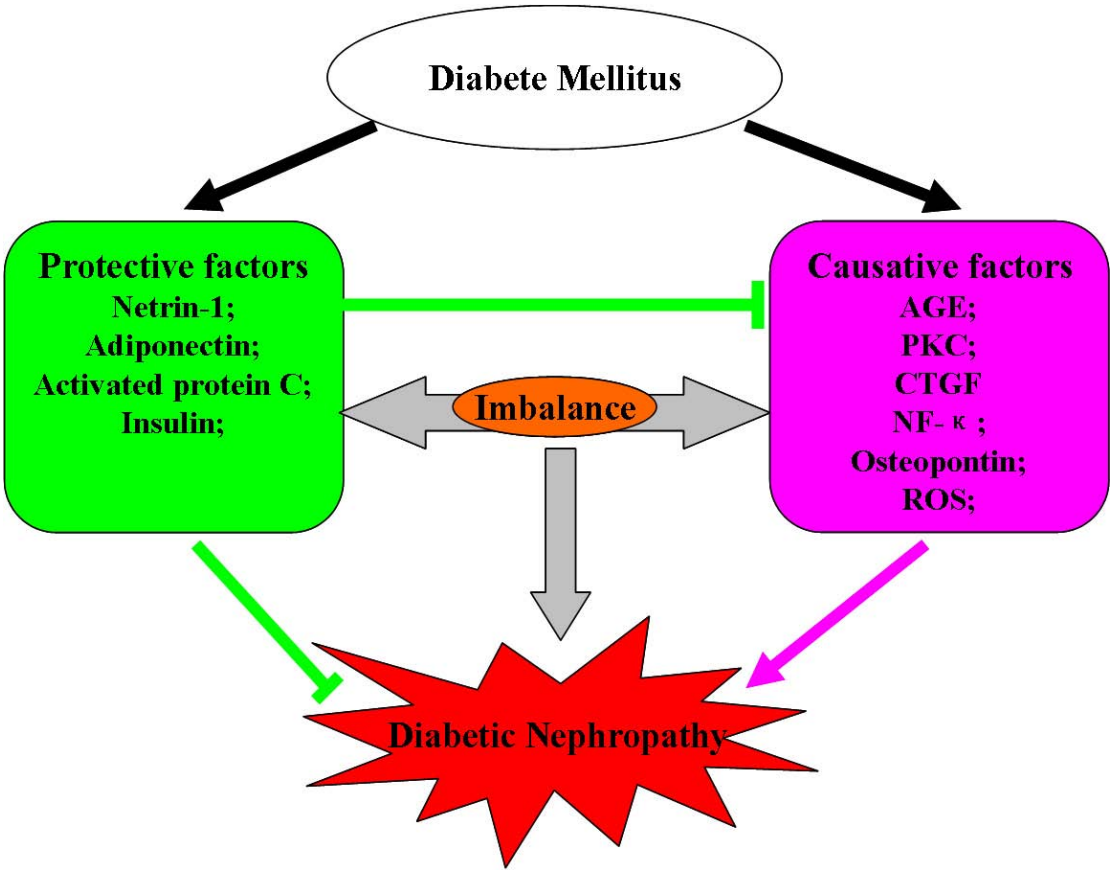

Figure1: Selected Causative and Protective Factors Determining Development of Diabetic Nephropathy
AGE, advanced glycation end-products; PKC, protein kinase C; CTGF: connective tissue growth factor; NF-κB: nuclear factor kappa B; ROS: reactive oxygen species

II. Causative Factors

The most significant changes which characterize DN include glomerular and tubular hypertrophy, thickening of the peripheral glomerular basement membrane, mesangial expansion, glomerulosclerosis and tubulointerstitial fibrosis [11]. These structural changes occurs as a result of an interaction between hemodynamic and metabolic factors, and finally lead to increased glomerular filtration rate (GFR), proteinuria, systemic hypertension and the loss of renal function (4, 12). Numerous efforts have been made to study the major causative molecules or pathways which include AGE, PKC, NF-κB, CTGF, ROS, Osteopontin (Fig. 2).

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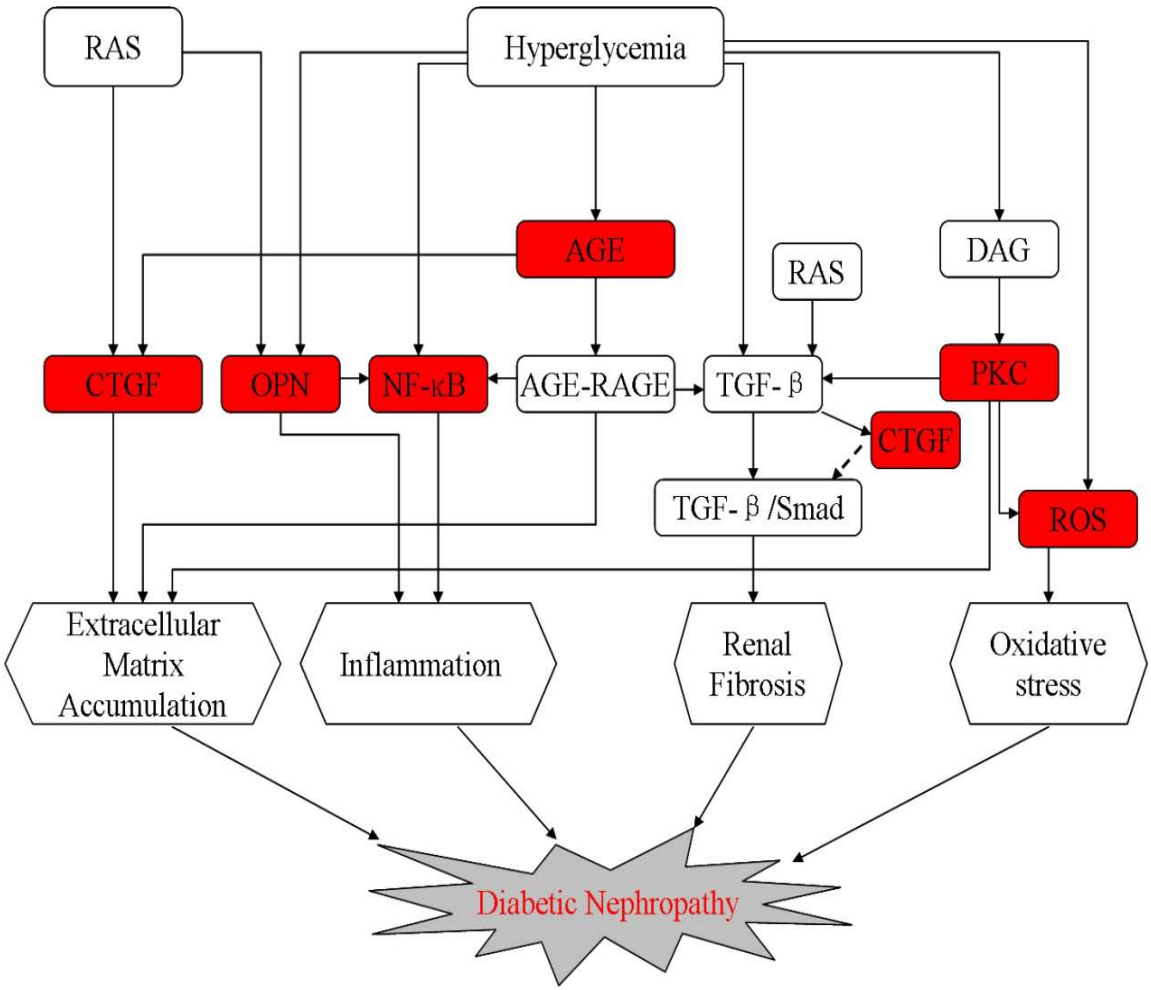

Figure 2 : Possible factors involved in induction and progression of diabetic nephropathy. RAS, rennin angiotensin system; AGE, advanced glycation end products; DAG, diacylglycerol; PKC, protein kinase C; CTGF, connective tissue growth factor; NF-κB, nuclear factor Kappa B; OPN, osteopontin; ROS, reactive oxygen species; TGF-β, transformed growth factor β

a) Advanced Glycation end Products

Advanced glycation end products (AGEs) as a result of chronic hyperglycemia and oxidative stress have been postulated to play major roles not only in the development of DN, but also in a range of cardiovascular complications [13, 14]. It is reported that AGE exert toxicity via three mechanisms: deposition, in situ glycation and receptor interaction [6]. Among these three mechanisms, the interactions between AGEs and their receptors (RAGE) play a major role in the progress of DM, especially DN. Its receptor is expressed on the surface of kidneys endothelial cells, podocytes, monocytes/macrophages, tubular and mesangial cells [15, 16]. Binding of AGEs to the RAGE on these cell types will stimulate oxidative stress generation, activate intracellular molecules such as PKC, TGF-β, VEGF and NF-κB, evoke inflammatory and fibrogenic reactions, thereby causing progressive alteration in renal architecture and loss of renal function in DN [6, 17]. The function of AGE-RAGE signaling pathway in the progress of DN has been proved by using the double transgenic mice mode which over expresses both iNOS and RAGE [18]. In this study, transgenic mice developed glomerular lesions rapidly, which could be prevented by AGEs inhibitor [18]. Soulis et al. (1996) initiated a research which also confirmed the beneficial effect of an AGE inhibitor Aminoguanidine in reducing the AGEs levels in blood and tissue of diabetic rats [19]. Similar beneficial effect was observed by using alagebrium, a putative AGEs cross-link breaker, to treat DM rodent model [20]. However, clinical trials for these AGE inhibitors were stopped due to toxicity of these inhibitors [21]. Thus, these studies provide further evidence that AGEs is a promising therapy target for DN and efforts should be made to find new inhibitor of AGEs for treatment of DN.

b) Protein Kinase c

Protein kinase C (PKC) belongs to the family of serine threonine kinase that act as an intracellular signal transduction system for many hormones and cytokines

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[22]. PKC has 15 different isoforms, many of which have been indicated to be involved in diabetic complications [9]. Among 15 isoforms of PKC, α, β, and δ isoforms have been most consistently implicated in DN. In DN, PKC isoforms, activated by enhanced diacylglycerol (DAG) and increased activity of polyol pathway, involves in numerous cellular pathways including NADH, ROS, Na+/K+ ATPase, AngⅡ, MAPK, VEGF, TGF-β and finally leads to series of physiological and structure changes such as endothelial dysfunction, glomerular basement membrane thickening, extracellular matrix accumulation, mesangial expansion, renal tubular fibrosis and glomerulosclerosis [9, 10, 23].

A range of novel compounds has been recently examined to inhibit PKC dependent pathways in DN. Ruboxistaurin, a selective inhibitor of the PKC-β, could normalize glomerular hyperfiltration, attenuate histological injury and functional decline, and reduce TGF-β levels and proteinuria [24]. A randomized clinical study has been carried out, in which the patients with DN took ruboxistaurin orally for one year. The study showed that DN patients treated with ruboxistaurin daily had a 24% greater decline in albuminuria than those given the placebo, and they had a stable estimated glomerular filtration rate as well [25]. In a recent study conducted by Bhattacharya et al. (2013), it was found that the upregulation and activation of PKC isoforms α, β, and δ in the renal tissue of diabetes rats play a detrimental role in the pathogenesis of DN by accumulating of extracellular matrix through upregulation of TGF-β, fibronectin and type Ⅳ collagen [23]. Treatment of diabetic rat with D-Saccharic acid 1, 4-lactone (DSL) could help to ameliorate alloxan-induced upregulation of PKC isoforms α, β, and δ as well as the accumulation of fibronectin and collagen [23]. Thus, strategies to target PKC pathway using isoform-specific inhibitors could be one of the promising therapeutic options, but well-designed large and long-term clinical studies are needed to establish its efficacy for prevention and treatment of DN.

c) Connective Tissue Growth Factor

Connective tissue growth factor (CTGF), known as insulin-like growth factor-binding protein 8 (IGFBP8) and CCN2, is increasingly being implicated in structural and functional changes of diabetic renopathy [26]. It is reported that the expression level of CTGF increased in glomerular and tubular of diabetes patients, and elevated in both early and late DN in humans [27]. CTGF, stimulated by both hyperglycemia related factors, such as AGEs, and hemodynamic stimuli such as angiotensin [28, 29], is involved in mesangial cell hypertrophy, accumulation of extracellular matrix, epithelial-to-mesenchymal transition of tubular cells [27]. CTGF is also a fibrogenic cytokine in the kidney and it is known to be a downstream mediator of the profibrotic effects of TGF-β inducing renal fibrosis [30, 31]. In TGF-β mediated renal fibrosis, the activated type 1 receptor of TGF-β phosphorylates and activates members of the receptor-Smads (R-Smads; Samd2 and Smad 3) which then form oligomers with the co-Smad and regulate the expression of target genes in nucleus; Smad7, an inhibitory Smad, prevents the recruitment and phosphorylation of Smad2 and Smad3 [12]. Several studies indicated that CTGF plays a central role in promoting the TGF-β/Smad signaling activity by decreasing the availability of smad7, which is inhibitory for Smad2 and 3 [27, 32]. In an animal model of unilateral ureteral obstruction (UUO), it was found that CTGF antisense treatment could attenuate tubulointerstitial fibrosis which further confirms the role of CTGF on TGF-β inducing renal fibrosis [33]. In a study conducted by Adler et al (2010), it was found that FG-3019, a humanized anti-CTGF monoclonal antibody, could decrease albuminuria of diabetic patients with incipient nephropathy effectively [34]. These studies demonstrate that strategies specifically targeting CTGF to retard the development of renal disease are likely to be an excellent therapeutic strategy for DN, although prospective studies are lacking.

d) Nuclear Factor Kappa b

Nuclear factor Kappa B (NF-κB), a transcription factor, plays an important role in cell survival and its inhibition leads to apoptosis. In the latent state, NF-κB is sequestered in the cytosol by its inhibitor IκB [35]. Upon stimulations, its inhibitor IκB will be phosphorylated and degraded rapidly. Proteasomal degradation of IκB ultimately frees NF-κB which then translocates into nuclear and activates targeted gene [35]. Numerous studies indicated that NF-κB is important modulator of diabetic complications, especially in DN [36, 37]. It is reported that NF-κB could be activated by a range of stimuli including high glucose, AGEs and ROS [38]. And activated NF-κB in turn regulates numerous genes including cytokines, adhesion molecules, NO synthase, angiotensinogen and other inflammatory factor implicated in the process of DN [39]. In addition, recent studies have indicated that NF-κB plays a key role in podocyte apoptosis [40], modulates the TGF-β intracellular signaling pathways [41], which provide further evidence for the role of NF-κB in the pathogenesis of DN. In a study conducted by Chiu et al. (2009), the typical characteristics of DN including mesangial expansion, accumulation of extracellular matrix were observed in rats injected with streptozotocin [42]. After treating these diabetic rats with curcumin, an inhibitor of NF-κB, these diabetes-associated abnormalities were ameliorated. Similar beneficial effects were observed by using Polydatin and Lycopene, the putative inhibitors of NF-κB signal pathway, to treat DN rats induced by streptozotocin [43, 44]. However, approaches to inhibit NF-κB have not been explored fully in clinical studies, most likely due to the intimate

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involvement of this transcription factor in a number of essential cellular processes including apoptosis.

e) Osteopontin

Osteopontin (OPN), also known as secreted phosphoprotein 1, is a complex secreted glycoprotein that facilitates cell adhesion and migration by binding integrins with its RGD domain [45]. OPN has also been shown to play a prominent role in inflammation via promoting macrophage retention and activating macrophage [46]. Its role in DN has recently been examined in OPN gene knockout mice [47]. It was found that diabetic OPN null mice have decreased albuminuria, glomerular extracellular matrix, mesangial area and TGF-β compared with their respective diabetic OPN+/+ littermates [47], which indicates that OPN promotes diabetic renal injury in diabetic OPN+/+ mice. Besides, the upregulated expression of OPN in human and mice with diabetes has been observed [48, 49]. And OPN, induced by hyperglycemia and lipopolysaccharides [49], is expressed in all glomerular cells including mesangial cells, podocytes, and endothelial cells [50, 51]. These results suggest that OPN contributes to DN via damage the glomerular cells. Lorenzen et al. (2008) carried out an experiment to investigate the molecular mechanism of OPN on cultured podocytes [49]. They found that OPN could activate NF-κB pathway, increase the expression of urokinase plasminogen activator and matrix metalloprotease, and finally lead to increased podocyte motility. The similar study was conducted by Nicholas et al. (2010) in which the effect of OPN on cultured mouse mesangial cells was studied [47]. The result shows that OPN could promote the accumulation of glomerular extracellular matrix through upregulating TGF-β, ERK/MAPK and JNK/MAPK signaling. They also found that the expression of TGF-β induced by glucose was inhibited by OPN antibodies. Thus, OPN seems to be a critical contributor to the pathogenesis of DN. However, further studies will be needed to validate whether OPN is truly a causative factor for DN or not.

f) Reactive Oxygen Species

High reactive oxygen species (ROS), induced by hyperglycemia, plays a prominent role in the pathogenesis of diabetic complications, especially DN [52, 53]. It is reported that ROS could be produced by various types of cells which include endothelial cells, mesangial cells, podocytes, tubular epithelial cells under hyperglycemic [1, 54]. Produced ROS are capable of disturb physiological function of these cells both directly, by oxidizing and damaging cellular macromolecules such as DNA, protein lipid and carbohydrate, and indirectly through the stimulation of multiple pathways, such as PKC, polyol pathways, NF-κB, RAAS, and accumulation of AGEs [52, 55]. Zhang et al. (2012) investigated the role of NADPH oxidase-derived ROS in cultured mesangial cell and found that high glucose could upregulate NADPH oxidase through JNK/NF-κB pathway and consequently produce ROS which finally contributes to glomerular mesangial cell proliferation and fibronectin expression [52]. They also use resveratrol, a polyphenolic phytoalexin, to treat high glucose induced mesangial cell and the results showed that resveratrol could inhibit mesangial cell expansion and fibronectin expression through blocking JNK/NF-κB/NADPH oxidase/ROS signaling pathways [52]. In another study, schizandrin, a blocker of NADPH oxidize-induced ROS signaling, was utilized to treat murine mesangial cell cultured in high glucose media [56]. The result showed that schizandrin inhibits high glucose induced mesangial cell proliferation and ECM over-expression through attenuating ROS level. Furthermore, a large number of experimental studies have proved the beneficial effect of antioxidants, such as Vitamins C and E, superoxide dismutase, and catalase, in ameliorating DN [57]. However, it is also reported that ROS are involved in the regulation of renal hemodynamic and renal ion transport which is the key for maintaining basic function of kidney [58, 59]. Therapeutic effect of ROS in preventing of DN is still debatable at this time.

III. Endogenous Protective Factors

The role of endogenous protective factors in the development of DN has been investigated widely. In a clinical research conducted by Perkins et al. (2003), 368 type 1 diabetic patients with microalbuminuria were followed up for 12 years [60]. It was found that, among these diabetic patients, more than 60% of type 1 diabetic patients were free from significant diabetic complications which suggest the presence of endogenous protective factors. Meanwhile, these results indicate that endogenous protective factors protect the diabetic patients from the progression of DN via neutralizing effect of risk factors such as PKC, ROS, TGF-β etc.

a) Netrin-1

The netrin-1, a diffusible laminin-related secreted protein, is originally identified as a neuronal guidance cue which directs neurons and their axons to targets during the development of the nervous system [61]. Recent investigations indicate that netrin-1 is highly expressed in many tissues outside the nervous system, especially in vascular endothelial cells of kidney to attenuate inflammation [62]. An investigation conducted by Wang et al. (2008) showed that downregulation of netrin-1 correspond with the increased expression of MCP-1 and IL-6 and infiltration of leukocytes into the kidney [63]. Mice with partial netrin-1 deficiency experience more severe degree of ischemic kidney injury because of exacerbated inflammation [64]. Meanwhile, it is also reported that administration of

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recombinant netrin-1 in kidney could suppress inflammation and apoptosis in vivo [65].

DN is a manifestation of an ongoing chronic low-grade inflammation [66]. The role of netrin-1 in DN has been investigated recently and the result showed that over-expression of netrin-1 could protect transgenic mice during DN via attenuating inflammation [67]. In a study conducted by Tak et al. (2013), partial netrin-1 deficiency mice mode (Ntrn 1+/-) was introduced to investigate the role of netrin-1 protein in STZ induced diabetic mice [68]. The result showed that Ntrn 1+/- mice revealed a more severe degree of DN compared with wild-type mice [68]. In addition, they found that treatment of DN with netrin-1 was associated with attenuated albuminuria and improved histological scores for DN. However, as most of these studies were done in animal model, further studies in clinic would be important to investigate its therapeutic function.

b) Adiponectin

Adiponectin, known as ACRP30 and GBP28, is an adipokine produced by white adipocytes and encoded by the APM1 gene in humans and rodents [69]. It has two receptors, AD1POR1 and ADIPOR2 which have been found to be widely expressed in liver, kidney, and endothelial cells [70]. Through interacting with its receptors AD1POR1 and ADIPOR2, adiponectin could mediate increased 5'adenosine monophosphate-activated protein kinase (AMPK) and activate peroxisome proliferator-activated receptor alpha (PPARα), respectively [70]. Recently investigation indicated that adiponectin have insulin-sensitizing effects which include stimulation of fatty acid oxidation and glucose uptake in skeletal muscle and suppression of glucose production in the liver via activating of AMPK in the peripheral tissue [71, 72]. They found that administration of adiponectin could lower circulating glucose levels without stimulating insulin secretion in both healthy and diabetic mice [72].

Besides, it is reported that adiponectin has a renoprotective effect in chronic renal disease including DN [73, 74]. In an experiment conducted by Ohahsi et al. (2007), the result showed that urine albumin excretion, glomerular hypertrophy and tubulointerstitial fibrosis were significantly worse in adiponectin knockout mice compared to wild type after performing subtotal (5/6) nephrectomy [74]. Further study demonstrated that adiponectin knockout mice developed podocyte foot process effacement which is a key process involved in the initial development of albuminuria [75]. Sharma et al. (2008) also reported that administration of adiponectin to knockout mice could help normalize albuminuria and restore podocytes foot process effacement via activating of AMPK in podocytes [75].

These finding strongly supports the importance of adiponectin as a renoprotective factor. However, it is still unclear whether adiponectin will provide significant effects toward human DN.

c) Activated Protein c

Protein C, known as an anticoagulant factor, is activated by binding of thrombin to its receptor, thrombomodulin. After activation, it is reported that protein C confers cytoprotective effect in various disease models, including DN [76, 78]. In diabetic patients and diabetic mice model, the function of endothelial thrombomodulin protein C system, which is in charge of activating protein C, is impaired and the level of activated protein C is reduced correspondingly [76, 77]. The study conducted by Isermann et al., (2007) also reported that the reduction of activated protein C in diabetic mice is responsible for the initiation of DN and maintaining high activated protein C level could protect glomerular filtration barrier by preventing glucose-induced apoptosis in endothelial cells and podocytes [76]. Besides, it is also reported that activated protein C have anti-inflammatory and fibrinolytic effects [79, 80]. In unilaterally nephrectomized C57/B16 diabetic mice model, the urine total protein to creatinine ratio, proteinurine and renal fibrosis were ameliorated by administration of exogenous activated protein C [80]. They also indicated that the concentration of causative factors such as monocyte chemoattractant protein-1 (MCP-1), TGF-β1 and CTGF were decreased significantly in APC-treated mice compared with untreated mice [80]. Thus, APC appears to be a protective factor with anti-apoptosis, anti-inflammatory and fibrinolytic effects for DN and clinical studies are needed to validate its therapeutic role.

d) Insulin

Insulin is an important vasotropic factor which regulates the function of vascular cells, such as endothelial cells, macrophages, and podocytes, via binding to its receptors on these cells [10]. After binding to its receptors, insulin can activate the pathway of insulin receptor substrate (IRS)/PI3K/Akt/endothelial NO synthase (eNOS) and stimulate the production of NO which results in vasodilatation and anti-thrombosis in the short term, and can inhibit smooth muscle cell growth and migration chronically [81, 82]. It is also reported that insulin could increases the expression of VEGF in several cell types, which in turn act as survival factor of podocytes, endothelial cells, and mesangial cells [83]. Furthermore, the studies indicated that insulin could prevent apoptosis through inhibition of transcription factor FoxO [84] and the proapoptotic molecule caspase-9 [85], or by upregulation of antioxidant activity of heme oxygenase-1 (HO-1) [86].

Impairment of insulin action has been recognized in diabetic glomeruli and leads to DN in diabetic animal model [87]. Recent study conducted by Welsh et al. (2010) reported that mice with gene knockout of the insulin receptor targeted to podocytes

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developed albuminuria, effacement of podocytes foot processes, increased deposition of components of the basal membrane, and a higher frequency of programmed podocytes apoptosis compared to control animals [88]. The pathology was quite similar to that seen in DN. Thus, this finding strongly supports the importance of insulin signaling as a renoprotective factor and improving insulin sensitivity in glomerular tissue may decrease the risk for DN.

IV. Conclusions

DN is a multifactorial disease including hemodynamic, metabolic, and inflammatory factors which are central to the development and progression of DN. Though strict glycaemic control and inhibitors of the renin angiotensin system are widely used in clinical therapy for DN, their beneficial effects are limited. Recent investigations indicated that inhibitors of causative factors such as AGE, PKC, CTGF, NF-κB and ROS could provide useful targets for therapy. Meanwhile, recognition of important endogenous protective factors against the development of DN is providing a new perspective for understanding the development of DN. Thus, understanding mechanisms of both causative and endogenous protective factors will open new avenues for possible therapeutic intervention (Fig. 1). In the near future, further studies are required to investigate the effects of various interventions modulating causative factors and endogenous protective factors in treatment of DN.

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Plasma Uric Acid Levels in Relation to Plasma Cholesterol Levels in Type-2 Diabetes Mellitus

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Abstract- Uric acid, the prime end product of purine catabolism, has been implicated in diabetes mellitus as well as in hyperlipidemias. Its significance in diabetic hypercholesterolemia is not established. A study was under taken to assess the relationship of plasma cholesterol with plasma uric acid in type-2 diabetes mellitus subjects. A fasting blood sample was collected from normal as well as type-2 diabetic subjects, the separated plasma was employed for the estimation of glucose, cholesterol and uric acid levels. It is observed that there is a proportional rise in uric acid in type-2 diabetic subjects, suggesting that plasma uric acid levels along with total cholesterol levels aids to asses the diabetes induced dyslipidemia as well as to control the diabetic dyslipidemia induced complications in type-2 diabetes mellitus.

Keywords: plasma uric acid,plasma cholesterol,type-2 diabetes mellitus, vascular complications.

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PLASMAURICACIDLEVELSINRELATIONTOPLASMACHOLESTEROLLEVELSINTYPE2DIABETESMELLITUS

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Plasma Uric Acid Levels in Relation to Plasma Cholesterol Levels in Type-2 Diabetes Mellitus

Goudappala Prashanthkumar[1] , Nagendra S[2] & Kashinath R T[3]

Abstract- Uric acid, the prime end product of purine catabolism, has been implicated in diabetes mellitus as well as in hyperlipidemias. Its significance in diabetic hypercholesterolemia is not established. A study was under taken to assess the relationship of plasma cholesterol with plasma uric acid in type-2 diabetes mellitus subjects. A fasting blood sample was collected from normal as well as type-2 diabetic subjects, the separated plasma was employed for the estimation of glucose, cholesterol and uric acid levels. It is observed that there is a proportional rise in uric acid in type-2 diabetic subjects, suggesting that plasma uric acid levels along with total cholesterol levels aids to asses the diabetes induced dyslipidemia as well as to control the diabetic dyslipidemia induced complications in type-2 diabetes mellitus.

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I. Introduction

Uric acid, the prime end product of purine catabolism is implicated in diabetes mellitus. Suggesting a possible role of insulin in nucleotide metabolism. It has been claimed by few research workers that plasma uric acid levels are elevated in diabetes mellitus (1-11).In earlier report from our laboratory the uric acid elevation in diabetes mellitushas been conclusively established as due to raised nucleotide catabolism (12).

The hyperglycemia observed in diabetes mellitus if not controlled may lead to various life threatening complications including micro and macro vascular diseases (13). A proper control, hence becomes the priority of management of diabetes mellitus. It is known that in dyslipidemia, one of the general complications ofdiabetes mellitusplasmatotal cholesterol levels are seen elevated (14). Further it is shown by few research workers thatplasma uric acid levels are elevated in hyperlipidemias including hypercholesterolemia. The present work was carried out in type 2 diabetic subjects to establish the inter relationship of plasma uric acid levels with diabetes induced Hypercholesterolemia.

II. Materials and Methods

The type-2 diabetic subjects (both male and females) attending the medical Out Patient Department of Subbaiah Medical College Hospital, Purle, Shimoga. were randomly selected, similarly normal subjects (both male and females) were randomly taken from employees of medical college and hospital. Fasting blood samples were collected from normal as well as selected diabetic subjects (The subjects having orthopedic & renal problems were excluded from the study) and were allowed to clot and plasma samples were separated by centrifugation at 3500rpm for 8mins, the separated samples were employed for estimation of Total Cholesterol (15) , Uric acid(16) and Glucose(17).

The results obtained were statistically analyzed using student t-test.

III. Results

The diabetic subjects were divided into two groups depending on their plasma cholesterol level. Group 1-NormoCholesterolemic Diabetic Subjects-having plasma cholesterol levels<200mg/dl and Group 2-HypercholsterolemicDiabetic Subjects-having plasma cholesterol levels >200mg/dl.The results obtained in the present study are given in Table-1 and Table-2

Table-1 narrates fasting plasma glucose levels as well as plasma uric acid levels in normal subjects and in type-2 diabetic subjects. It is evident from the table that uric acid levels are significantly elevated ($p<0.001$) in type2 diabetic subjects as compared to normal.

Table-2 depicts the values of plasma total cholesterol and plasma uric acid levels in group1 diabetic subjects (plasma cholesterol<200mg/dl) and in group2 diabetic subjects (plasma cholesterol >200mg/dl). It is clear from the table that there is significant elevation in plasma uric acid levels in hypercholesterolemic subjects as compared to normal cholesterolemic subjects.

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Table 1 : Table showing fasting plasma levels of glucose and uric acid in normal subjects as well as in type-2 diabetic subjects.

	Fasting Plasma Glucose mg/dl	Uric acid mg/dl
Normals (11)	103.82 ± 13.80	3.688 ± 0.732
Diabetics (58)	196.93*** ± 15.03	7.033*** ± 1.700

Note:

1. *The Values are expressed as their Mean ±S.D*
2. *The number in parenthesis indicate the number of subjects.*
3. *Statistical significance is given by *p>0.05,**p>0.01,***p>0.*

Table 2 : Table showing fasting plasma levels of cholesterol and uric acid in normocholesterolemicdiabetic subjects (plasma cholesterol <200mg/dl) as well as hyper cholesterolemic diabetic subjects (plasma cholesterol>200mg/dl).

	Plasma Cholesterol mg/dl	Plasma Uric acid mg/dl
Normo Cholesterolemic Diabetic subjects (25)	159.56 ± 22.99	5.676 ± 0.829
Hyper Cholesterolemic Diabetic subjects (29)	252.90*** ± 40.69	8.203*** ± 1.348

Note:

1. *The Values are expressed as their Mean ±S.D*
2. *The number in parenthesis indicate the number of subjects.*
3. *Statistical significance is given by *p>0.05,**p>0.01,***p>0.001*

IV. Discussion

Uric acid, the end product of purine catabolism in humans, has been suggested to have a close relationship with cardiovascular diseases , where an increase in plasma uric acid levels have been observed (18-20). Further it has been shown that plasma uric acid levels are elevated in hyperlipidemia specifically hypertriglyceridemia (21-23). The elevated plasma uric acid levels observed in our present studies are in agreement with our earlier reports(1-11) as well as with earlier findings (12) and the rise observed may be due to increased purine turnover as suggested in our earlier communication from our laboratory (12) or may be due to diabetic dyslipidemia induced increased vascular damage(13) A parallel increase in plasma uric acid levels along with plasma cholesterol levels in the present study in type-2 diabetic subjects suggests a possible relationship between plasma uric acid level and plasma lipid profile specifically plasma cholesterol. Kelley and Palella (24) have observed a rise in uric acid levels in hypertriglyceridemia ,hypertension, obesity and diabetes mellitus (24,25)

The increase observed in uric acid levels in the present studies indicates a definite rise in uric acid levels in diabetic subjects with a close relationship to cholesterol levels. The observed increase in uric acid levels in type-2 diabetic subjects indicates a positive relationship of uric acid levels with cholesterol levels in type-2 subjects(refer Table-2) suggesting, the rise in uric acid parallel increases in cholesterol levels. Many life threatening complications of type-2 diabetes mellitus specifically micro angiopathy have been attributed to diabetes induced dyslipidemia. As there is a parallel rise in uric acid along with cholesterol levels in type-2 diabetic subjects an estimation of uric acid levels in serum may be an additional significant criteria to assess dyslipidemia as well as to control the dyslipidemia induced complications in type-2 diabetes mellitus. Hence we conclude the plasma uric acid estimation

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along with serum total cholesterol levels seems highly beneficial in type-2 diabetic subjects to asses the diabetic dyslipidemia induced vascular complications.

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	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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