ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2016 June 25; 7(12): 243-259

Published by Baishideng Publishing Group Inc

WJD World Journal of Diabetes

A peer-reviewed, online, open-access journal of diabetes

Editorial Board

2016-2019

The *World Journal of Diabetes* Editorial Board now consists of 676 members, representing a team of worldwide experts in diabetes mellitus. They are from 56 countries, including Argentina (1), Australia (26), Austria (9), Belgium (5), Brazil (11), Canada (24), Chile (3), China (39), Cuba (1), Czech Republic (2), Denmark (12), Egypt (3), Finland (5), France (11), Germany (26), Greece (16), Hungary (4), Iceland (1), India (24), Iran (6), Iraq (2), Ireland (4), Israel (9), Italy (54), Japan (30), Jordan (1), Kuwait (3), Lebanon (1), Malaysia (1), Malta (1), Mexico (4), Netherlands (7), New Zealand (3), Nigeria (2), Norway (2), Oman (3), Pakistan (2), Poland (8), Portugal (1), Qatar (1), Romania (2), Singapore (4), Slovakia (1), South Africa (1), South Korea (15), Spain (25), Sweden (6), Switzerland (3), Thailand (4), Tunisia (1), Turkey (13), United Arab Emirates (3), United Kingdom (28), United States (199), Venezuela (2), and Yemen (1).

Subrata Chakrabarti, *London*
David ZI Cherney, *Toronto*
Mervyn Deitel, *Toronto*
Jean-Pierre Despres, *Québec*
David J Hill, *Ontario*
Tian-Ru Jin, *Toronto*
Arulmozhi D Kandasamy, *Alberta*
Jennifer L Kuk, *Toronto*
Ismail Laher, *Vancouver*
Zhong-Cheng Luo, *Montreal*
Roger S McIntyre, *Toronto*
David Meyre, *Hamilton*
JF Ndisang, *Saskatoon*
Raj S Padwal, *Alberta*
Ciriaco A Piccirillo, *Montreal*
AM James Shapiro, *Edmonton*
Guang Sun, St. *John's*
Valerie Taylor, *Ontario*
Cory Toth, *Calgary*
André Tremblay, *Montréal*
VVincent C Woo, *Manitoba*
James R Wright, *Alberta*
Xi-Long Zheng, *Calgary*

Chile

Sebastian S Martin, *Valparaiso*
Armando Rojas Rubio, *Talca*
Luis Sobrevia, *Santiago*

China

Jie Chen, *Nanjing*
Bernard Man Yung Cheung, *Hong Kong*
William CS Cho, *Hong Kong*
Tian-Pei Hong, *Beijing*
Qin Huang, *Shanghai*
Po-Sing Leung, *Hong Kong*
Chao Liu, *Nanjing*
Jian-Kang Liu, *Xi'an*
Lie-Gang Liu, *Wuhan*
Ronald CW Ma, *Hong Kong*
Zengchang Pang, *Qingdao*
Jin-Sheng Qi, *Shijiazhuang*
Jin-Xiong She, *Shijiazhuang*
Wing Y So, *Hong Kong*
Cheuk C Szeto, *Hong Kong*
Kathryn CB Tan, *Hong Kong*
Cong-Yi Wang, *Wuhan*
Yu Wang, *Hong Kong*
Guang-Da Xiang, *Wuhan*
Bao-Feng Yang, *Harbin*
Shu-Yu Yang, *Xiamen*
Xi-Lin Yang, *Hong Kong*
Zai-Qing Yang, *Wuhan*
Shan-Dong Ye, *Hefei*
Shi-Sheng Zhou, *Dalian*
Zhi-Guang Zhou, *Changsha*

Cuba

Luis Sarmiento-Pérez, *Havana*

Czech Republic

Michal Krcma, *Plzen*
Terezie Pelikanova, *Prague*

Denmark

Charlotte Brons, *Gentofte*
Flemming Dela, *Copenhagen N*
Kristine Faerch, *Gentofte*
Louise G Grunnet, *Gentofte*
R Scott Heller, *Gentofte*
Filip K Knop, *Hellerup*
Helle Markholst, *Måløv*
Ole H Mortensen, *Copenhagen N*
Oluf Pedersen, *Copenhagen K*
Esben T Vestergaard, *Aarhus N*
Milan Zdravkovic, *Soborg*

Egypt

Mamdouh MA Hssan, *Dokki*
Moshira AH Rateb, *Cairo*
Mona F Schaalan, *Cairo*

Finland

Siamak Bidel, *Helsinki*
Gang Hu, *Helsinki*
Thomas Kietzmann, *Oulu*
Qing Qiao, *Espoo*
Karoliina Wehkalampi, *Helsinki*

France

Jean C Ansquer, *Dijon*
Bertrand Cariou, *Nantes*
Sylvie Dejager, *Rueil-Malmaison*
Naim A Khan, *Dijon*
Jean-Philippe Lavigne, *Nimes*
Michel Marre, *Paris*
Marie-Claude Morice, *Massy*
Riccardo Perfetti, *Paris*
Gérard Said, *Paris*
Didier Vieau, *Villeneuve*
Sophie Visvikis-Siest, *Nancy*

Germany

Christa Buechler, *Regensburg*
Roland Büttner, *Heidelberg*
Michael Froehner, *Dresden*
Ioanna Gouni-Berthold, *Cologne*
Hammes Hans-Peter, *Mannheim*
Nadja Herbach, *Munich*
Nadj Herbach, *Munchen*
Andrea Icks, *Düsseldorf*
Thomas Jax, *Neuss*
Michael Kluge, *Munich*
Florian Lang, *Tuebingen*
Matthias Laudes, *Koln*
Ralf Lobmann, *Stuttgart*
Rafael T Mikolajczyk, *Bremen*
Andreas S Mueller, *Halle*
Karsten Müssig, *Tübingen*
Nahid Parvizi, *Mariensee*
Thomas P Reinehr, *Datteln*
Michael Ristow, *Jena*
Sven Schinner, *Duesseldorf*
Peter EH Schwarz, *Dresden*
Ovidiu A Stirban, *Oeynhausen*
Diego J Walther, *Berlin*
Silvia A Wein, *Kiel*
Christian Wrede, *Berlin*
Dan Ziegler, *Düsseldorf*

Greece

George P Chrousos, *Athens*
Moses S Elisaf, *Ioannina*
Panagiotis Georgoulias, *Larissa*
Nikolaos Kadoglou, *Thessaloniki*
Gerasimos E Krassas, *Krini*
Spilios Manolakopoulos, *Athens*
Peppa Melpomeni, *HalDari*
Nikolaos Papanas, *Alexandroupolis*
Dimitrios Papazoglou, *Alexandroupolis*
Sokratis Pastromas, *Athens*
Christina Piperi, *Goudi*
Nicholas K Tentolouris, *Athens*
Konstantinos A Toulis, *Salonika*
Apostolos Tsapas, *Thessaloniki*
Konstantinos Tziomalos, *Thessaloniki*
Elias Zintzaras, *Larissa*

Hungary

Mária Bagyánszki, *Szeged*
Gyorgy Jermendy, *Budapest*
Karoly Racz, *Budapest*
Gyula Soltesz, *Pécs*

Iceland

Saher Hamed, *Haifa*

India

Sarika Arora, *New Delhi*
Pitchai Balakumar, *Sivakasi*
Muthuswamy Balasubramanyam, *Chennai*
Anuradha Carani Venkatraman, *Nagar*
Subhabrata Chakrabarti, *Hyderabad*
Abhay S Chakraborti, *Kolkata*
Tapan K Chaudhuri, *New Delhi*
Kanwaljit Chopra, *Chandigarh*
Malabika Datta, *Delhi*
Debidas Ghosh, *West Bengal*
Ravinder Goswami, *New Delhi*
Jothydev Kesavadev, *Kerala*
KVS H Kumar, *Lucknow*

Anoop Misra, *New Delhi*
Analava Mitra, *Kharagpur*
Viswanathan Mohan, *Chennai*
Pallavi Panchu, *Bangalore*
Deepak N Patel, *Mumbai*
Usharani Pingali, *Hyderabad*
Ambady Ramachandran, *Chennai*
Vadde Ramakrishna, *Kadapa*
Rajat Sandhir, *Chandigarh*
Manju Sharma, *New Delhi*
Suman B Sharma, *Delhi*

Iran

Mohammad K Arababadi, *Rafsanjan*
Leila Azadbakht, *Isfahan*
Hamid Baradaran, *Tehran*
Behrooz Broumand, *Tehran*
Majid Ghayour-Mobarhan, *Mashhad*
Mohsen Janghorbani, *Isfahan*

Iraq

Saad AR Hussain, *Baghdad*
Abbas A Mansour, *Basrah*

Ireland

Amar Agha, *Dublin*
Michael Aviram, *Haifa*
Raymond E Farah, *Safed*
Mark P Hehir, *Dublin*

Israel

Gal Dubnov-Raz, *Hashomer*
Shimon Efrat, *Tel Aviv*
Oren Froy, *Rehovot*
Farid M Nakhoul, *Lower Galilee*
Orit Pinhas-Hamiel, *Ramat-Gan*
Eleazar Shafrir, *Jerusalem*
Gerald H Tomkin, *Dublin*
Haim Werner, *Tel Aviv*
Marina S Zimlichman, *Holon*

Italy

Luigi A Angrisani, *Napoli*
Roberto Baldelli, *Rome*
Giuseppe Barbaro, *Rome*
Alessandro Bartolomucci, *Parma*
Giuseppina Basta, *Pisa*
Simona Bertoli, *Milano*
Federico Bilotta, *Rome*
Fabio Broglio, *Torino*
Riccardo Calafiore, *Perugia*
Sergio Coccheri, *Bologna*
Massimo Collino, *Torino*
Marco A Comaschi, *Genoa*
Renzo Cordera, *Genova*
Francesco Dotta, *Siena*
Fiorucci Fiorucci, *Perugia*
Maurizio Galderisi, *Naples*
Amalia Gastaldelli, *Pisa*
Ezio Ghigo, *Turin*
Carla Giordano, *Palermo*
Paolo Gisondi, *Verona*
Riccarda Granata, *Turin*
Giorgio Iervasi, *Pisa*
Claudia Kusmic, *Pisa*
Francesco Landi, *Rome*
Monica R Loizzo, *Cosenza*
Paolo Magni, *Milan*
Mariano Malaguarnera, *Catania*
Melania Manco, *Rome*
Giulio M Marchesini, *Bologna*
Piero Marchetti, *Pisa*
Massimo Massi-Benedetti, *Perugia*
Moschetta Moschetta, *Bari*
Antonio E Nicolucci, *Milano*
Lucia Pacifico, *Rome*
Stefano Palomba, *Reggio Emilia*
Giampaolo Papi, *Carpi*
Renato Pasquali, *Bologna*
Piermarco M Piatti, *Milano*
Dario Pitocco, *Rome*
Antonio E Pontiroli, *Milano*
Manfredi Rizzo, *Palermo*
Carmelo L Rosa, *Catania*
Raffaella Rosso, *Genoa*
Giuseppe Schillaci, *Perugia*
Leonardo A Sechi, *Sassari*
Imad Sheiban, *Verona*
Cesare R Sirtori, *Milano*
Giovanni Tarantino, *Naples*
Giovanni Targher, *Verona*
Francesco G Tieh, *Chieti*
Donadon Valter, *Pordenone*
Alberto Verrotti, *Chieti*
Andrea Viggiano, *Napoli*
Gian V Zuccotti, *Milan*

Japan

Masato Asahina, *Chiba*
Takuya Awata, *Tochigi*
Yuichiro Eguchi, *Saga*
Goji Hasegawa, *Kyoto*
Satoshi Inoue, *Tokyo*
Eiji Ishimura, *Osaka*
Masayuki Iwano, *Nara*
Takashi Kadowaki, *Tokyo*
Eisuke Kagawa, *Hiroshima*
Masahito Katahira, *Nagoya*
Eiji N Kawasaki, *Nagasaki*
Noriyuki Koibuchi, *Gunma*
Kazuhiko Kotani, *Tochigi*
Daisuke Koya, *Ishikawa*
Norikazu Maeda, *Osaka*
Takayuki Masaki, *Oita*
Yuji Matsuzawa, *Osaka*
Kazuaki Nishio, *Tokyo*
Kenji Okumura, *Nagoya*
Motoaki Saito, *Yonago*
Toshiyasu Sasaoka, *Toyama*
Michio Shimabukuro, *Okinawa*
Kohzo Takebayashi, *Saitama*
Hiroyuki Tamemoto, *Abiko*
Takashi Togo, *Yokohama*
Jun Udagawa, *Izumo*
Yoshinari Uehara, *Fukuoka*
Takuya Watanabe, *Tokyo*
Toshihiko Yada, *Tochigi*
Tohru Yorifuji, *Kyoto*

Jordan

Yousef S Khader, *Irbid*

Kuwait

Kamal AAS Al-Shoumer, *Surra*
Ibrahim F Benter, *Safat*
Abu S Mustafa, *Safat*

Lebanon

Ramzi F Sabra, *Beirut*

Malaysia

Mafauzy Mohamed, *Kota Bharu*

Malta

Charles Savona-Ventura, *Msida*

Mexico

Manuel Gonzalez-Ortiz, *Guadalajara*
Fernando Guerrero-Romero, *Dgo*
Jesus A Olivares-Reyes, *Mexico*
Rocío Salceda, *Mexico*

Netherlands

Sander Kersten, *Wageningen*
Nanne Kleefstra, *Zwolle*
Edwin CM Mariman, *Maastricht*
Frans Pouwer, *Tilburg*
Han Roelofsen, *Groningen*
Suat Simsek, *Alkmaar*
Marcel T Twickler, *Halsterseweg*

New Zealand

Paul Hofman, *Auckland*
Peter E Lobie, *Grafton*
Elaine Rush, *Auckland*

Nigeria

Adejuwon A Adeneye, *Ikeja*
Anthonia O Ogbera, *Ikeja*

Norway

Akhtar Hussain, *Oslo*
Odd E Johansen, *Hovik*

Oman

Jumana S Saleh, *Muscat*
Mohammed A Shafaee, *Muscat*
Radha Shenoy, *Muscat*

Pakistan

Shahid Hameed, *Islamabad*
Jamil A Malik, *Islamabad*

Poland

Marcin Baranowski, *Bialystok*
Jerzy Beltowski, *Lublin*
Alicia H Dydejczyk, *Krakow*
Maciej Owecki, *Poznań*
Ewa Pankowska, *Warsaw*
Agnieszka Piwowar, *Wroclaw*
Dorota A Zieba, *Krakow*

Portugal

Graca M Pereira, *Braga*

Qatar

Hong Ding, *Doha*

Romania

Elena Ganea, *Bucharest*
Adriana Georgescu, *Bucharest*

Singapore

Thameem T Dheen, *Singapore*
Yung-Seng Lee, *Singapore*
Daniel PK Ng, *Singapore*
Rob M van Dam, *Singapore*

Slovakia

Katarína Šebeková, *Bratislava*

South Africa

Md S Islam, *Durban*

South Korea

Hueng-Sik Choi, *Gwangju*
Kyung M Choi, *Seoul*
Won M Hwang, *Seoul*
Eui-Bae Jeung, *Cheongju*
Ju-Hee Kang, *Incheon*
Sin-Gon Kim, *Seongbuk-Gu*
Sung-Jin Kim, *Seoul*
Young-Gyu Ko, *Seoul*
Kang-Beom Kwon, *Chonbuk*
Sangyeoup Lee, *Yangsan*
Myung Gull Lee, *Gyeonggi-Do*
Soo Lim, *Seongnam*
Byung-Hyun Park, *Jeonbuk*
Seungjoon Park, *Seoul*
Jeesuk Yu, *Chungnam*

Spain

Vivencio Barrios, *Madrid*
M. Luisa Bonet, *Palma de Mallorca*
Justo P Castano, *Cordoba*
Manuel A Diosdado, *Cádiz*
Javier Espino, *Badajoz*
Ricardo V García-Mayor, *Vigo*
José M Gómez-Sáez, *Barcelona*
Oreste Gualillo, *Santiago de Compostela*
Emilio Herrera, *Madrid*
Amelia Marti, *Pamplona*
Navarra JA Martínez, *Pamplona*
Maria L Martinez-Chantar, *Derio*
Merce Miranda, *Tarragona*
Alberto Ortiz, *Madrid*
Maria J Ramirez, *Pamplona*
Eugenia Resmini, *Barcelona*
Pedro Romero-Aroca, *Reus*
Jordi Salas-Salvado, *Reus*
Gines M Salido, *Caceres*
Victor Sanchez-Margalet, *Seville*
Helmut Schroder, *Barcelona*
Carmen Segundo, *Cadiz*
Rafael Simo, *Barcelona*
Manuel Vazquez-Carrera, *Barcelona*

Sweden

Joanna Hlebowicz, *Malmö*
Peter Lindgren, *Stockholm*
Kaj S Stenlof, *Göteborg*
Ann-Britt Wirehn, *Linköping*
Wei-Li Xu, *Stockholm*
Shao-Nian Yang, *Stockholm*

Switzerland

Kaspar Berneis, *Zurich*
Kim-Anne Le, *Lausanne*
Christian Toso, *Geneva*

Thailand

Narattaphol Charoenphandhu, *Bangkok*
Arthorn Riewpaiboon, *Bangkok*
Rawee Teanpaisan, *Hat-Yai*
Viroj Wiwanitkit, *Bangkok*

Tunisia

Khaled Hamden, *Sfax*

Turkey

Ugur Cavlak, *Denizli*
Teoman Dogru, *Etlik*
Ersin Fadillioglu, *Ankara*
Abdurrahman F Fidan, *Afyonkarahisar*
Muammer Karadeniz, *Bornova-Izmir*
Cevde Kaya, *Istanbul*
Fahrettin Kelestimur, *Kayseri*
Altan Onat, *Istanbul*
Semir Ozdemir, *Antalya*
Mustafa Sahin, *Ankara*
Ilker Tasci, *Ankara*
Belma Turan, *Ankara*
Serap Yalin, *Mersin*

United Arab Emirates

Ernest Akingunola Adeghate, *Al Ain*
Mukesh M Agarwal, *Al Ain*
Samir M Awadallah, *Sharjah*

United Kingdom

Nisreen Alwan, *Leeds*
Bing Chen, *Liverpool*
Fay Crawford, *Edinburgh*
Timothy M Curtis, *Belfast*
Umesh Dashora, *Edinburgh*
Gareth W Davison, *Belfast*
Peter Flatt, *Coleraine*
Kathleen M Gillespie, *Bristol*
Peter J Grant, *Leeds*
Lorna W Harries, *Exeter*
Nigel Hoggard, *Aberdeen*
Nigel Irwin, *Coleraine*
Pappachan Joseph, *London*
Andreas F Kolb, *Aberdeen*
Moffat J Nyirenda, *Edinburgh*
Jeetesh V Patel, *Birmingham*
Snorri B Rafnsson, *Edinburgh*
Thozhukat Sathyapalan, *Yorkshire*
Latika Sibal, *Newcastle*
Rajagopalan Sriraman, *Lincoln*
Ramasamyiyer Swaminathan, *London*
Abd A Tahrani, *Birmingham*
Neil G Thomas, *Birmingham*
Cecil Thompson, *London*
Paul H Whiting, *Leicester*

United States

Varun Agrawal, *Springfield*

Pascale Alard, *Louisville*
Omar Ali, *Milwaukee*
Mohamed AS Al-Shabrawey, *Augusta*
Judith Aponte, *New York*
Balamurugan N Appakalai, *Louisville*
Hwyda A Arafat, *Philadelphia*
Carl V Asche, *Salt Lake City*
Sanford A Asher, *Pittsburgh*
Anthony Atala, *Winston-Salem*
Sami T Azar, *New York*
George L Bakris, *Chicago*
Alistair J Barber, *Hershey*
Daniel C Batlle, *Chicago*
David SH Bell, *Birmingham*
Rita Bortell, *Worcester*
Sebastien G Bouret, *Los Angeles*
Donald W Bowden, *Winston-Salem*
David L Brown, *Stony Brook*
Jack D Caldwell, *Erie*
Anna C Calkin, *Los Angeles*
Roberto A Calle, *Groton*
Keith R Campbell, *Pullman*
Carlos Campos, *New Braunfels*
Heping Cao, *New Orleans*
Krista Casazza, *Birmingham*
Aaron B Caughey, *Portland*
Eileen R Chasens, *Pittsburgh*
Munmun Chattopadhyay, *Ann Arbor*
Xiao-Li Chen, *St Paul*
Craig I Coleman, *Hartford*
Robert Conley, *Indianapolis*
Colleen Croniger, *Cleveland*
Doyle M Cummings, *Greenville*
William C Cushman, *Memphis*
Patricia Darbishire, *West Lafayette*
Guillaume Darrasse-Jèze, *New York*
Ravi KM Dasu, *Sacramento*
Michael H Davidson, *Chicago*
Prakash Deedwania, *San Francisco*
Hong-Wen Deng, *Kansas City*
Teresa P DiLorenzo, *Bronx*
Scot Dowd, *Lubbock*
Samuel Durso, *Baltimore*
Krystal Edwards, *Dallas*
Alexander M Efanov, *Indianapolis*
Azza B El-Remessy, *Augusta*
Amy Z Fan, *Atlanta*
Melissa S Faulkner, *Tucson*
George S Ferzli, *Staten Island*
Paolo Fiorina, *Boston*
James E Foley, *East Hanover*
Samuel N Forjuoh, *Temple*
Alessia Fornoni, *Miami*
Trudy Gaillard, *Columbus*
Pietro Galassetti, *Irvine*
Claudia Gragnoli, *Hershey*
Jennifer B Green, *Durham*
Alok K Gupta, *Piscataway*
Gary J Grover, *Piscataway*
Werner Gurr, *New Haven*
Samy L Habib, *San Antonio*
Abdel Hamad, *Baltimore*
Tiffany Hilton, *Pittsford*
Michael F Holick, *Boston*
Zhaoyong Hu, *Houston*
Rachel Hudacko, *Suffern*
Yasuo Ido, *Boston*
Brian K Irons, *Lubbock*
Pamela Itkin-Ansari, *La Jolla*
Hieronim Jakubowski, *Newark*
Hong-Lin Jiang, *Blacksburg*
Ping Jiao, *Providence*
Shengkan Jin, *Piscataway*
Arpita Kalla, *St Louis*
Richard E Katholi, *Springfield*
Melina R Kibbe, *Chicago*
Bhumsoo Kim, *Ann Arbor*
Tomoshige Kino, *Bethesda*
Julienne K Kirk, *Winston-Salem*
Renu A Kowluru, *Detroit*
Lewis H Kuller, *Pittsburgh*
Rajesh Kumar, *Temple*
Blandine Laferrere, *New York*
Cong-Jun Li, *Beltsville*
Ching-Shwun Lin, *San Francisco*
James F List, *Princeton*
Dongmin Liu, *Blacksburg*
Zhen-Qi Liu, *Charlottesville*
Maria F Lopes-Virella, *Charleston*
Cai Lu, *Louisville*
George W Lyerly Jr, *Conway*
Jian-Xing Ma, *Oklahoma City*
Xin-Laing Ma, *Philadelphia*
Rong Ma, *Fort Worth*
David Maggs, *San Diego*
Kenneth Maiese, *Newark*
Kevin C Maki, *Glen Ellyn*
Sridhar Mani, *Bronx*
Suresh Mathews, *Auburn*
Lauraar R McCabe, *East Lansing*
Sarah Messiah, *Miami*
Thomas O Metz, *Richland*
Shannon Miller, *Orlando*
Murielle Mimeault, *Omaha*
Raghu G Mirmira, *Indianapolis*
Prasun J Mishra, *Bethesda*
Reema Mody, *Grayslake*
Arshag D Mooradian, *Jacksonville*
Mohammad-Reza Movahed, *Tucson*
Yingjun J Mu, *Rahway*
Nair G Muraleedharan, *East Lansing*
Manuel F Navedo, *Seattle*
Charles B Nemeroff, *Atlanta*
Joshua J Neumiller, *Spokane*
Steven J Nicholls, *Cleveland*
Hirofumi Noguchi, *Dallas*
Craig S Nunemaker, *Charlottesville*
Patrick J O'Connor, *Minneapolis*
Wei-Hong Pan, *Baton Rouge*
Naushira Pandya, *Fort Lauderdale*
Michael R Peluso, *Corvallis*
Inga Peter, *New York*
Axel Pflueger, *Rochester*
Gretchen A Piatt, *Pittsburgh*
John D Piette, *Ann Arbor*
Leonid Poretsky, *New York*
Parviz M Pour, *Omaha*
Wei Qiu, *Boston*
Teresa Quattrin, *Buffalo*
Cristina Rabadán-Diehl, *Bethesda*
Rajendra S Raghow, *Memphis*
Swapnil N Rajpathak, *Bronx*
Armin Rashidi, *Norfolk*
Mohammed S Razzaque, *Boston*
Beverly AS Reyes, *Philadelphia*
Shuo L Rios, *Los Angeles*
David Rodbard, *Potomac*
Helena W Rodbard, *Rockville*
June H Romeo, *Cleveland*
Raul J Rosenthal, *Florida*
Juan M Saavedra, *Bethesda*
Frank AJL Scheer, *Boston*
Richard E Scranton, *Tiverton*
Vallabh R Shah, *Albuquerque*
Aziz Shaibani, *Houston*
Guo-Ping Shi, *Boston*
Carol A Shively, *Winston-Salem*
Anders AF Sima, *Detroit*
Rajan Singh, Los *Angeles*
Pramil N Singh, *Loma Linda*
Dawn D Smiley, *Atlanta*
Matthew D Solomon, *Stanford*
Rakesh K Srivastava, *Tyler*
Bangyan L Stiles, *Los Angeles*
Erin St Onge, *Apopka*
Yu-Xiang Sun, *Houston*
Salim Surani, *Corpus Christi*
Arthur LM Swislocki, *Martinez*
Ya-Xiong Tao, *Auburn*
John A Tayek, *Torrance*
John G Teeter, *New Haven*
Carlos M Telleria, *Vermillion*
Christophe G Thanos, *Providence*
Ronald G Tilton, *Galveston*
Serena Tonstad, *Loma Linda*
Michael Traub, *Staten Island*
Margrit Urbanek, *Chicago*
Vladimir N Uversky, *Indianapolis*
Gabriel Uwaifo, *Baton Rouge*
Volker Vallon, *San Diego*
Shambhu D Varma, *Baltilmore*
Chengming Wang, *Auburn*
Hong-Jun Wang, *Boston*
Mark E Williams, *Boston*
Guang-Yu Wu, *New Orleans*
Zhong-Jian Xie, *San Francisoco*
Ming-Zhao Xing, *Baltimore*
Hariom Yadav, *Bethesda*
Lijun Yang, *Gainesville*
Ruojing Yang, *Rahway*
Subhashini Yaturu, *Albany*
Joseph Yeboah, *Charlottesville*
Dengping Yin, *Nashville*
Yi-Sang Yoon, *Rochester*
Yi-Hao Yu, *New York*
Kevin CJ Yuen, *Portland*
Ian S Zagon, *Hershey*

Robert YL Zee, *Boston*
Cui-Lin Zhang, Rockville
James X Zhang, Richmond
Sarah X Zhang, Oklahoma City
Guixiang Zhao, *Atlanta*
Yang Zhao, *Carmel*

Ming-Hui Zou, *Oklahoma City*

Venezuela

José F Arévalo, *San Bernardino*

Fuad Lechin, *Caracas*

Yemen

Khaled AA Ahmed, *Ibb*

World Journal of Diabetes

Contents

Biweekly Volume 7 Number 12 June 25, 2016

REVIEW

243 Daily physical activity and type 2 diabetes: A review

Hamasaki H

ORIGINAL ARTICLE

Retrospective Cohort Study

252 Does parity worsen diabetes-related chronic complications in women with type 1 diabetes?

Gomes MB, Negrato CA, Almeida A, de Leon AP

World Journal of Diabetes
Volume 7 Number 12 June 25, 2016

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Carlos Campos, MD, Staff Physician, Private Practice, Practicing Family Physician in New Braunfels, New Braunfels, TX 78130, United States

AIM AND SCOPE

World Journal of Diabetes (*World J Diabetes*, *WJD*, online ISSN 1948-9358, DOI: 10.4239), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJD covers topics concerning α, β, δ and PP cells of the pancreatic islet, the effect of insulin and insulinresistance, pancreatic islet transplantation, adipose cells and obesity.

We encourage authors to submit their manuscripts to *WJD*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ ABSTRACTING

World Journal of Diabetes is now indexed in Emerging Sources Citation Index (Web of Science), PubMed, and PubMed Central.

FLYLEAF **I-VI** Editorial Board

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
March 15, 2010

FREQUENCY
Biweekly

Xiu-Xia Song, Vice Director
World Journal of Diabetes
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
June 25, 2016

World Journal of Diabetes

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4239/wjd.v7.i12.243

World J Diabetes 2016 June 25; 7(12): 243-251
ISSN 1948-9358 (online)

REVIEW

Daily physical activity and type 2 diabetes: A review

Hidetaka Hamasaki

Hidetaka Hamasaki, Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, Chiba 272-8516, Japan

Hidetaka Hamasaki, Hamasaki Clinic, Kagoshima 890-0046, Japan

Author contributions: Hamasaki H wrote the review.

Conflict-of-interest statement: No conflict of interest.

Manuscript source: Invited manuscript

Correspondence to: Hidetaka Hamasaki, MD, PhD, Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, 1-7-1 Kohnodai, Chiba 272-8516, Japan. hhamasaki78@gmail.com
Telephone: +81-47-3723501
Fax: +81-47-3721858

Received: January 26, 2016
Peer-review started: January 27, 2016
First decision: March 23, 2016
Revised: April 5, 2016
Accepted: May 7, 2016
Article in press: May 9, 2016
Published online: June 25, 2016

Abstract

Physical activity improves glycemic control and reduces the risk of cardiovascular disease (CVD) and mortality in patients with type 2 diabetes (T2D). Moderate to vigorous physical activity is recommended to manage T2D; however, patients with T2D can be physically weak, making it difficult to engage in the recommended levels of physical activity. Daily physical activity includes various activities performed during both occupational and leisure time such as walking, gardening, and housework that type 2 diabetic patients should be able to perform without considerable physical burden. This review focuses on the association between daily physical activity and T2D. Walking was the most common form of daily physical activity, with numerous studies demonstrating its beneficial effects on reducing the risk of T2D, CVD, and mortality. Walking for at least 30 min per day was shown to reduce the risk of T2D by approximately 50%. Additionally, walking was associated with a reduction in mortality. In contrast, evidence was extremely limited regarding other daily physical activities such as gardening and housework in patients with T2D. Recent studies have suggested daily physical activity, including non-exercise activity thermogenesis, to be favorably associated with metabolic risks and mortality. However, well-designed longitudinal studies are warranted to elucidate its effects on overall health.

Key words: Type 2 diabetes; Daily physical activity; Walking; Non-exercise activity thermogenesis

Core tip: In addition to moderate- to vigorous-intensity exercise, daily physical activity is also important for the prevention and management of type 2 diabetes (T2D). Of note, individuals can engage in daily physical activity without remarkable physical burden, anywhere and at any time. It is well known that exercise improves the outcomes of metabolic diseases and reduces cardiovascular disease risk and mortality. However, the literature pertaining to the effects of specific types of daily physical activity on health is sparse. It is necessary to accumulate evidence on the positive effects of daily physical activity on the management of T2D.

review. *World J Diabetes* 2016; 7(12): 243-251 Available from: URL: http://www.wjgnet.com/1948-9358/full/v7/i12/243.htm DOI: http://dx.doi.org/10.4239/wjd.v7.i12.243

INTRODUCTION

Exercise therapy is essential for the management of diabetes. A sedentary lifestyle is known to be a major risk factor of cardiovascular disease (CVD)[1]. The American College of Sports Medicine and the American Diabetes Association have recommended at least 150 min/wk of moderate (50%-70% of an individual's maximum heart rate) to vigorous (> 70% of an individual's maximum heart rate) physical activity for patients with type 2 diabetes (T2D)[2]. As for patients with type 1 diabetes, regular physical activity has also shown beneficial effects on glycemic control and other health-related outcomes, although the evidence is limited[3].

However, the recommended intensity and duration of exercise could present a physical burden to diabetic patients and lead to cessation of exercise therapy because diabetic patients have a lower physical performance threshold than healthy individuals. Patients with T2D show a lower energy expenditure, number of steps, and duration of physical activity compared to subjects without diabetes[4], as well as low cardiorespiratory fitness[5,6]. Moreover, the muscle strength of individuals with T2D is significantly lower than those without[7,8]. In fact, upper and lower extremity muscle strength have been shown to be inversely associated with the degree of diabetic complications[9], suggesting that diabetes progression hinders engagement in physical activity. Indeed, the percentage of patients with diabetes found to engage in exercise therapy was approximately 40%[10], and only 28.2% of diabetic patients in the United States achieved the recommended level of physical activity[11]. In a large-scale cohort study, individuals who performed low-volume physical activity, which was defined as 15 min/d or 90 min/wk, had a 14% reduced risk of all-cause mortality and a life expectancy increase of 3 years[12]. Thus, it is important to note that in addition to moderate- to vigorous-intensity physical activity, light- to moderate-intensity daily physical activity should also be considered an alternative and supportive exercise therapy regimen for diabetic individuals.

The purpose of this review is to highlight the effects of daily physical activity on health in type 2 diabetic patients and to further suggest a strategy for the treatment of T2D by changing the amount of daily physical activity a patient performs. This review will help physical therapists, clinicians, and patients manage T2D.

DAILY PHYSICAL ACTIVITY

Daily physical activity is defined as continuous bodily movements via the contraction of skeletal muscle that results in an increase in energy expenditure in daily life[13]. This includes various activities that are conducted in both occupational and leisure time such as walking, working at a desk, washing, cooking, and sports. On the other hand, exercise is defined as planned, structured, and repetitive physical activity that has the objective of improving physical fitness[13]. Physical activity is usually classified by its intensity and duration. The metabolic equivalent (MET) is a useful measurement for representing the intensity of physical activity and is defined as the amount of oxygen uptake while sitting at rest. An oxygen uptake of 3.5 mL/kg per minute is equal to the basal resting metabolic rate and is considered to be 1 MET[14]. Ainsworth *et al*[15] listed MET values for 821 specific physical activities that vary in their intensity of daily physical activity according to the situation in which they are performed. For example, walking inside is equal to only 2.0 METs (light intensity) whereas walking with children is the equivalent of 4.0 METs (moderate intensity). Therefore, it should be noted that daily physical activity covers a wide range of intensity that at times are the same as structured exercise (Table 1).

SEDENTARY LIFESTYLE

Sedentary behavior refers to the tendency to sit during waking hours with low energy expenditures. The mean sitting time is estimated to be approximately 6-7 h/d in developed countries, and a decreased level of physical activity has been shown to be inversely associated with increased sitting time[16]. In today's world, individuals are more prone to sit on a daily basis.

Whose lifestyle is healthier: A person who engages in the recommended amount of exercise during their leisure time but is extremely sedentary in their spare time, or a person who does not achieve the recommended level of physical activity but is quite physically active in the workplace? The answer: Exercise and sedentary behavior may be mutually contradictory[17]. Sedentary time has been recognized as an independent risk factor for CVD, T2D, and all-cause mortality[17-19]. The American Diabetes Association has recommended that patients with diabetes should be encouraged to reduce their sedentary time and to not sit for more than 90 min[20]. Changing one's sedentary lifestyle to a more active lifestyle is key to the better management of T2D. In addition, sitting time may not affect all-cause mortality if it is combined with walking time, suggesting that the positive association between sitting time and mortality is only evident in individuals who sit for very long periods of time[21]. This review focuses on clinical studies that have investigated the effects of walking on CVD risk factors and mortality.

WALKING

Walking is one of the most common physical activities of daily life[22,23]. However, 54.6% of patients with T2D have reported engaging in no weekly physical activity through walking[24], demonstrating that patients with T2D should walk more frequently. Epidemiological studies have suggested that walking is associated

Table 1 Excerpt of various daily physical activities and their associated metabolic equivalents

Daily physical activity	METs
Walking	
Very slow, < 3.2 km/h	2
Slow, 3.2-4.0 km/h	2.8-3.0
For pleasure, moderate pace, 4.5-5.1 km/h	3.5
Brisk, 5.6 km/h	4.3
Very brisk, 6.4-7.2 km/h	5.0-7.0
Stair climbing, slow pace	4
Stair climbing, fast pace	8.8
Gardening	3.8
Yard work	3.0-6.0
Mowing lawn	5.5
Shoveling	5.3-7.5
Housework	
Washing dishes	1.8-2.5
Cleaning	2.3-3.8
Cooking	2.0-3.0
Child care	2.0-3.0
Elder care	2.3-4.0

Each activity is quoted from Ainsworth *et al*[15] (2011 Compendium Physical Activities). METs: Metabolic equivalents.

with a reduced risk of T2D. Hu *et al*[25] examined the relationship between physical activity, based on the use of a questionnaire, and the incidence of T2D in individuals selected from the Nurses' Health Study database. A total of 70102 women without diabetes were followed for 8 years. Overall, walking MET scores had a strong negative association with the risk of T2D. More specifically, a normal walking pace (3.2-4.8 km/h) was associated with an approximate 20%-30% reduction in the risk of T2D in women who did not engage in vigorous physical activity, and a faster walking pace was independently associated with a reduced risk of T2D. Moreover, Tanasescu *et al*[26] examined the relationship of walking with CVD risk and mortality among 3058 men with T2D. Frequent walking (≥ 16.1 MET-hours/week) was associated with a nearly 40% reduced risk of mortality, and walking pace was inversely associated with CVD and total mortality independent of walking hours. Gregg *et al*[27] also investigated whether walking reduced mortality among 2896 United States adults with diabetes. Patients who walked at least 2 h/wk had a 39% lower all-cause mortality rate and a 34% lower CVD mortality rate compared with sedentary patients. However, it is important to note that these studies were observational studies, and a causal relationship between walking and incidence of T2D and/or CVD cannot therefore be deduced. Moreover, physical activity, including the amount and speed of walking, might have been over or underestimated in these studies because physical activity was evaluated by questionnaires, and such subjective data are known to have poor validity[28], as eliminating bias is quite difficult. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research trial[29-31] investigated whether changes in ambulatory activity, assessed objectively through the use of a pedometer, were associated with a reduced risk of cardiovascular events in individuals with impaired glucose tolerance. During a 45211 person-years follow-up, ambulatory activity was found to be inversely associated with the risk of a cardiovascular event. Specifically, an increase of 2000 steps/d at baseline was associated with a 10% reduction in having a cardiovascular event, and a 2000-step increase in daily life from baseline to 12 mo was associated with an 8% lower cardiovascular event rate[32]. On the other hand, the Nakanojo Study[33] suggested that not just walking but the combination of walking (> 8000-10000 steps/d) and physical activity at an intensity > 3 METs was necessary to prevent metabolic syndrome. Daily physical activity that reaches an intensity > 3 METs may need to be emphasized. A list of published articles that focused on the beneficial association of walking with the risk of T2D, CVD, and mortality is shown in Table 2.

The Diabetes Prevention Program randomly assigned 3234 individuals with impaired glucose tolerance to one of three interventions: Standard lifestyle recommendations plus metformin treatment, standard lifestyle recommendations plus placebo, or an intensive program of lifestyle modification. The lifestyle intervention reduced the incidence of diabetes by 58% after a 2.8-year follow-up. Brisk walking for at least 150 min/wk was a very effective way to prevent T2D[34]. The Da Qing IGT and Diabetes Study investigated the effects of walking for at least 30 min/d on individuals with impaired glucose tolerance. A total of 577 subjects were randomized to one of three groups: Diet only, walking only, or diet plus walking. Over a 6-year follow-up, the incidence of diabetes was significantly reduced by 46% in the walking group[35]. Kosaka *et al*[36] showed that a lifestyle intervention for men with impaired glucose tolerance effectively reduced the risk of diabetes. They recommended the following activities to their subjects to increase their physical activity: Walking for 30-40 min/d, using a staircase instead of an elevator or an escalator, performing 30 min of cycling on weekends, and getting off a bus one stop before their destination. Their findings demonstrated that the physical activity intervention combined with diet therapy reduced the risk of diabetes by 67.4%. A list of published articles with a focus on the effects of walking on the risk of T2D is shown in Table 3.

Several small-scale intervention studies have revealed favorable effects of walking on CVD risk factors. A walking program of 1 h/d for 12 wk was shown to improve physical fitness, body composition, and glycemic control in postmenopausal women with T2D[37]. Similarly, walking at least 10000 steps/d combined with diet therapy in obese patients with T2D improved their insulin sensitivity[38]. Moreover, a meta-analysis of randomized controlled trials summarized the effects of walking on glycemic control and CVD risks; specifically, walking significantly decreased glycated hemoglobin levels by 0.50% (95%CI: -0.78% to -0.21%), body mass index by -0.91 kg/m^2 (95%CI: -1.22 to -0.59 kg/m^2),

Table 2 Epidemiological studies investigating the associations of walking with the risk of type 2 diabetes, cardiovascular events, and mortality

Ref.	Study design	Subjects	Physical activity measurement	Outcome, results
Hu *et al*[25]	Prospective cohort study	70102 female participants without diabetes, CVD, or cancer	MET score and walking pace based on a questionnaire	Risk of type 2 diabetes, normal walking pace (3.2-4.8 km/h): RR = 0.72; 95%CI: 0.62-0.85 Brisk or very brisk walking pace (> 4.8 km/h): RR = 0.41; 95%CI: 0.33-0.52
Tanasescu *et al*[26]	Prospective cohort study	3058 men with type 2 diabetes	MET-hour score measured by a questionnaire	Mortality, walking ≥ 16.1 MET-hours/week: RR = 0.60; 95%CI: 0.41-0.88 Very brisk walking pace (≥ 4 mph): RR = 0.42; 95%CI: 0.19-0.97
Gregg *et al*[27]	Prospective cohort study	2896 subjects with diabetes	Time spent walking measured by a questionnaire	Mortality, walking ≥ 2 h/wk, all-cause mortality: HRR = 0.61; 95%CI: 0.48-0.78; CVD mortality: HRR = 0.66; 95%CI: 0.45-0.96
Yates *et al*[32]	Prospective data analysis from the NAVIGATOR trial (a multicenter, randomized, placebo controlled, 2 × 2 factorial trial)	9306 individuals with impaired glucose tolerance	Number of steps assessed by a pedometer	Cardiovascular events, baseline ambulatory activity (2000 step/d increment): HR = 0.90; 95%CI: 0.84-0.96 Change in ambulatory activity from baseline to 12 mo (2000 step/d difference in change): HR = 0.92; 95%CI: 0.86-0.99

MET: Metabolic equivalents; RR: Relative risk; HRR: Hazard rate ratio; CVD: Cardiovascular disease; HR: Hazard ratio; NAVIGATOR: Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research.

Table 3 Clinical trials investigating the effects of walking on the risk of type 2 diabetes

Ref.	Study design	Subjects, follow-up time	Intervention	Results
Knowler *et al*[34]	Randomized clinical trial	3234 individuals with impaired glucose tolerance, 2.8 yr	A minimum of 150 min of physical activity similar intensity to brisk walking and 7% weight loss	58% reduction in the incidence rate of type 2 diabetes
Pan *et al*[35]	Randomized clinical trial	577 individuals with impaired glucose tolerance, 6 yr	At least 30 min/d of walking	46% reduction in the risk of developing diabetes
Kosaka *et al*[36]	Randomized clinical trial	458 men with impaired glucose tolerance, 4 yr	Recommendations for physical activity: walking 30-40 min/d, using staircase instead of an elevator or an escalator, 30-min cycling on weekends and getting off one bus stop before the destination	67.4% reduction in the risk of developing diabetes

and diastolic blood pressure by -1.97 mmHg (95%CI: -3.94 to -0.0 mmHg)[39]. Recently, an interesting study investigating postprandial changes in glucose, insulin, and non-esterified fatty acids in postmenopausal women at high risk of T2D was published. In this study, 22 participants were randomly assigned to one of six groups: Prolonged sitting (7.5 h) plus standing (total of 60 min), standing plus walking (total of 60 min), walking plus sitting, standing plus sitting, or walking plus standing. Both standing and walking significantly reduced postprandial glucose, insulin, and non-esterified fatty acids response compared with prolonged sitting[40]. Thus, diabetic patients may only need to stand to improve their metabolic profile.

Additionally, the way in which one walks may also be of significance. Karstoft *et al*[41] investigated the effects of interval-walking *vs* continuous-walking in patients with T2D. Four months of free-living interval-walking improved maximal oxygen consumption (VO_2 max), body composition, and glycemic control. VO_2 max significantly increased by 16.1%, fat mass and visceral fat significantly decreased by 10.8% and 10.6%, respectively, fasting insulin significantly decreased by 19.5%, and mean glucose concentrations measured by the continuous glucose monitoring system significantly decreased by 8.5% in the interval-walking group, whereas no changes were observed in the continuous-walking group. Their next study focused on determining whether interval-walking improved postprandial glucose tolerance and free-living glycemic control more than continuous-walking. Their findings revealed that a greater reduction in postprandial blood glucose levels was observed with a single interval-walking session than with an oxygen consumption- and time duration-matched continuous-walking session[42]. The optimal exercise therapy for individuals with T2D and existing diabetic complications is still unknown. The amount, duration, and intensity of exercise has been emphasized in diabetes care; however, the mode of physical activity such as the variation in intensity and motion may also need to be emphasized.

GARDENING, HOUSEWORK, AND OTHER ACTIVITIES

Gardening is the most popular daily physical activity in

older adults[43,44]; however, the current literature does not provide sufficient evidence of the health benefits of gardening[45]. The Evaluating Long-term Diabetes Self-management Among Elder Rural Adults study, a population-based cross-sectional study, described the types of daily physical activities performed among rural older adults with diabetes. The most common physical activities reported by these individuals were walking (79.7%), housework (68.7%), and gardening (64.8%). Health-related quality of life, as measured by the short form 12-item survey scale, has been found to be positively associated with physical activity, suggesting that participating in a greater amount of daily physical activity such as gardening and housework is beneficial for older adults[46]. As domestic physical activity, which includes gardening and housework, has been analyzed as a part of total daily physical activity in previous studies, it is difficult to determine its independent effects on health. However, it is important to investigate the effects of domestic physical activity on glycemic control, CVD risk, and mortality, as domestic chores are the main contributors to total daily physical activity in patients with T2D[47]. Stamatakis *et al*[48] examined the independent effects of domestic physical activity (*e.g.*, cleaning windows, sweeping, digging, cycling, dancing) on mortality and CVD events in the Scottish Health Survey. Participation in intense domestic physical activity was associated with lower all-cause mortality (men: RR = 0.68, 95%CI: 0.50-0.91; women: RR = 0.70, 95%CI: 0.52-0.93). A recent study showed that heavy housework was associated with reduced mortality (HR = 0.71; 95%CI: 0.56-0.91) and reduced cancer deaths (HR = 0.52) in older Chinese men[49]. However, the associations between domestic physical activity and mortality or CVD risk in diabetic patients were not investigated in these studies. In contrast, Lawlor *et al*[50] found that participating in at least 2.5 h of heavy housework was not associated with an improvement in obesity among elderly British women. However, this study also lacked information concerning T2D. There is extremely little evidence to suggest that gardening and/or housework have beneficial effects on mortality, CVD risk, or other metabolic disturbances in patients with T2D. Conversely, an observational study in healthy older adults objectively measured free-living activity energy expenditure by using the doubly labeled water method and demonstrated its association with a lower risk of mortality[51]. There was an approximate 30% lower risk of mortality for every 287 kcal consumed per day by free-living activity energy expenditure; however, self-reported high-intensity exercise did not differ between the activity energy expenditure tertiles, suggesting that light- to moderate-intensity daily physical activity plays a key role in healthy living. Beddhu *et al*[52] analyzed data from the 2003-2004 National Health and Nutrition Examination Survey and showed that the duration of light-intensity physical activity (*e.g.*, casual walking, light gardening, cleaning), objectively assessed by an accelerometer, was significantly associated with a lower mortality risk (HR = 0.59; 95%CI: 0.35-0.98) in the chronic kidney disease (CKD) population; however, an increase in moderate/vigorous activity duration did not result in a significantly lower hazard ratio in the CKD group. Approximately 20%-30% of patients with CKD had diabetes in this study, which suggests that light-intensity daily physical activity can reduce mortality in diabetic patients with CKD. Thus, these findings suggest that in contrast to moderate- to vigorous-intensity exercise, light-intensity daily physical activity may have beneficial health effects on diabetic patients who have progressed complications. Moreover, Steeves *et al*[53] conducted a study analyzing data from the 2003-2006 National Health and Nutrition Examination Survey and found that the total physical activity levels of patients with diabetes, as measured by an accelerometer, were significantly lower compared to participants with normal glucose tolerance and prediabetes. The diabetic participants were found to be inactive from 10:00 am to 8:00 pm when compared with participants with normal glucose tolerance, and their physical activity per hour declined rapidly after 12:00 pm, with the greatest difference occurring at 4:00 pm[53]. These findings suggest that clinicians should consider activity patterns in daily life as well as total physical activity to achieve optimal glycemic control in patients with T2D.

NON-EXERCISE ACTIVITY THERMOGENESIS

Daily physical activity, with the exception of volitional sports-like activities, is defined as non-exercise activity thermogenesis (NEAT)[54]. NEAT is the main determinant of variability in total daily energy expenditure[55], which varies substantially from person to person by up to 2000 kcal/d[56]. NEAT is influenced by various factors. For example, NEAT has been shown to increase by 25% seven days after a single bout of high-intensity walking exercise[57]. Moreover, regular exercise, especially moderate- to vigorous-intensity exercise, may increase NEAT; in contrast, living in an urban area populated with individuals who live a sedentary lifestyle will likely result in a decrease in NEAT. Indeed, the ambulation levels of rural Jamaicans was found to be more than 60% of those of urban North Americans, suggesting that urbanization is associated with a decrease in NEAT[58]. However, the intensity, frequency, and duration of physical activity required to increase NEAT is unknown. Furthermore, Levine *et al*[59] examined whether weight gain was associated with a decrease in walking distance. The consumption of an additional 1000 kcal/d significantly decreased walking distance in both lean and obese individuals, suggesting that weight gain due to overeating may result in decreased walking. Schmidt *et al*[60] examined whether 23 obesity-prone individuals and 32 obesity-resistant individuals had a different response to 3 d of overeating. They found that the walking time of

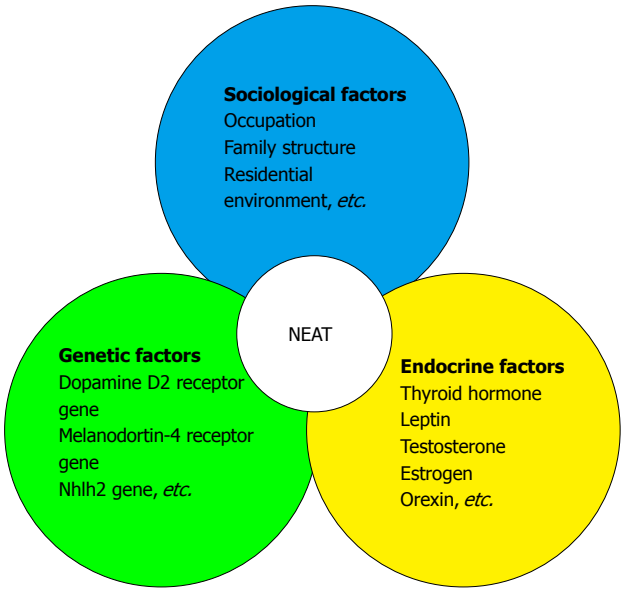

Figure 1 Non-exercise activity thermogenesis is intricately regulated by sociological, endocrinological, and genetic factors. NEAT: Non-exercise activity thermogenesis.

obesity-prone subjects decreased significantly (-2.0%), whereas obesity-resistant subjects maintained their walking time. Taken together, these studies collectively suggest that daily diet, exercise, and living environment all influence the amount of NEAT. Furthermore, endocrine factors such as thyroid hormones[61], leptin[62], sex steroids[63], and orexin[64] have all been shown to affect changes in NEAT. Several biological studies have also demonstrated that genetic variations exist in the propensity for spontaneous physical activity. For example, polymorphisms in the dopamine D2 receptor gene and melanocortin-4 receptor gene have been associated with physical activity variations in adults, and polymorphisms in the *Nhlh2* gene have shown effects on the motivation to exercise[65]. NEAT is thus modulated by endocrine, genetic, and sociological factors (Figure 1).

Previous studies have shown that NEAT plays a crucial role in the management of obesity[66]. The Look AHEAD (Action for Health in Diabetes) study did not find a reduction in the rate of cardiovascular events in obese patients with T2D after implementation of an intensive lifestyle intervention that aimed to achieve at least 7% weight loss by a reduction in dietary intake and a minimum of 175 min of moderate-intensity physical activity per week. This finding suggests that this lifestyle intervention should be conducted before an individual becomes obese[67]. Indeed, NEAT is a noteworthy factor in the management of obesity and other metabolic risks. The Shanghai Women's Health Study, a prospective cohort study, investigated the effects of exercise, walking and cycling for transportation, as well as the effect of non-exercise physical activity, on mortality. A total of 67143 women without a history of heart disease, stroke, or cancer were followed for an average of 5.7 years. That study found that women who reported 10 or more MET-hours per day of non-exercise activity had a 25%-50% lower risk of mortality compared with less active women[68]. Moreover, Hagger-Johnson *et al*[69] analyzed data from the United Kingdom Women's Cohort Study (1999-2002) to investigate the association between fidgeting behaviors and all-cause mortality. Data on sitting time and fidgeting behavior of 12778 women were analyzed. Among women in the low fidgeting group, sitting for $\geqslant$ 7 h/d (*vs* < 5 h/d) was associated with a 30% increase in risk of all-cause mortality. Among women in the high fidgeting group, sitting for 5-6 h/d was associated with a decreased mortality risk (HR = 0.63, 95%CI: 0.43-0.91)[69]. Fidgeting as a component of NEAT may reduce all-cause mortality; however, little evidence is available regarding the associations between NEAT and T2D. Hamasaki *et al*[70,71] previously reported that NEAT was associated with a reduction in waist circumference, improvement in insulin sensitivity and dyslipidemia, and an increase in B-type natriuretic peptide[72] levels in patients with T2D. However, a causal relationship between NEAT and the incidence of T2D could not be deduced, as attempting to conduct a prospective study with a high level of evidence would be quite difficult because, by definition, intervention studies for NEAT would not be practical when the effect of NEAT on metabolic disease is also unknown. As physical activity is no longer an intervention for NEAT, the development of new intervention strategies to target NEAT will be an issue that should be addressed in the future.

CONCLUSION

The current literature provides evidence of the efficacy of walking in preventing T2D and reducing the risk of cardiovascular events and/or mortality. More specifically, previous studies have suggested that brisk walking for at least 30 min/d (*e.g.*, $\geqslant$ 15 MET-hours per week) is needed to reduce the risk of T2D. Walking improves insulin sensitivity, glycemic control, and the incidence of obesity. However, there are few studies investigating the independent effects of other daily physical activities such as gardening and housework on health, especially in patients with T2D. The current literature lacks well-conducted controlled longitudinal studies investigating the effects of only daily physical activity on diabetes, dyslipidemia, hypertension, other CVD risks, and mortality. Daily physical activity, including NEAT, may be associated with a reduction in mortality. Although ensuring that patients with T2D engage in daily physical activity may be difficult, well-designed longitudinal studies that focus on daily physical activity independent of structured exercise should be conducted in the future.

REFERENCES

1 **Thompson PD**, Buchner D, Pina IL, Balady GJ, Williams MA,

Marcus BH, Berra K, Blair SN, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger NK. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation* 2003; **107**: 3109-3116 [PMID: 12821592 DOI: 10.1161/01.CIR.0000075572.40158.77]

2 **Colberg SR**, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, Chasan-Taber L, Albright AL, Braun B; American College of Sports Medicine; American Diabetes Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care* 2010; **33**: e147-e167 [PMID: 21115758 DOI: 10.2337/dc10-9990]

3 **Yardley JE**, Hay J, Abou-Setta AM, Marks SD, McGavock J. A systematic review and meta-analysis of exercise interventions in adults with type 1 diabetes. *Diabetes Res Clin Pract* 2014; **106**: 393-400 [PMID: 25451913 DOI: 10.1016/j.diabres.2014.09.038]

4 **Fagour C**, Gonzalez C, Pezzino S, Florenty S, Rosette-Narece M, Gin H, Rigalleau V. Low physical activity in patients with type 2 diabetes: the role of obesity. *Diabetes Metab* 2013; **39**: 85-87 [PMID: 23159129 DOI: 10.1016/j.diabet.2012.09.003]

5 **Cuff DJ**, Meneilly GS, Martin A, Ignaszewski A, Tildesley HD, Frohlich JJ. Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. *Diabetes Care* 2003; **26**: 2977-2982 [PMID: 14578226 DOI: 10.2337/diacare.26.11.2977]

6 **Ozdirenç M**, Biberoğlu S, Ozcan A. Evaluation of physical fitness in patients with Type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2003; **60**: 171-176 [PMID: 12757989 DOI: 10.1016/S0168-8227(03)00064-0]

7 **Sayer AA**, Dennison EM, Syddall HE, Gilbody HJ, Phillips DI, Cooper C. Type 2 diabetes, muscle strength, and impaired physical function: the tip of the iceberg? *Diabetes Care* 2005; **28**: 2541-2542 [PMID: 16186295 DOI: 10.2337/diacare.28.10.2541]

8 **Cetinus E**, Buyukbese MA, Uzel M, Ekerbicer H, Karaoguz A. Hand grip strength in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2005; **70**: 278-286 [PMID: 15878215 DOI: 10.1016/j.diabres.2005.03.028]

9 **Balducci S**, Sacchetti M, Orlando G, Salvi L, Pugliese L, Salerno G, D'Errico V, Iacobini C, Conti FG, Zanuso S, Nicolucci A, Pugliese G. Correlates of muscle strength in diabetes: The study on the assessment of determinants of muscle and bone strength abnormalities in diabetes (SAMBA). *Nutr Metab Cardiovasc Dis* 2014; **24**: 18-26 [PMID: 24095149 DOI: 10.1016/j.numecd.2013.04.010]

10 **Peyrot M**, Rubin RR, Lauritzen T, Snoek FJ, Matthews DR, Skovlund SE. Psychosocial problems and barriers to improved diabetes management: results of the Cross-National Diabetes Attitudes, Wishes and Needs (DAWN) Study. *Diabet Med* 2005; **22**: 1379-1385 [PMID: 16176200 DOI: 10.1111/j.1464-5491.2005.01644.x]

11 **Resnick HE**, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999-2002: the National Health and Nutrition Examination Survey. *Diabetes Care* 2006; **29**: 531-537 [PMID: 16505501 DOI: 10.2337/diacare.29.03.06.dc05-1254]

12 **Wen CP**, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, Chan HT, Tsao CK, Tsai SP, Wu X. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 2011; **378**: 1244-1253 [PMID: 21846575 DOI: 10.1016/S0140-6736(11)60749-6]

13 **Caspersen CJ**, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985; **100**: 126-131 [PMID: 3920711]

14 **Balducci S**, Sacchetti M, Haxhi J, Orlando G, D'Errico V, Fallucca S, Menini S, Pugliese G. Physical exercise as therapy for type 2 diabetes mellitus. *Diabetes Metab Res Rev* 2014; **30** Suppl 1: 13-23 [PMID: 24353273 DOI: 10.1002/dmrr.2514]

15 **Ainsworth BE**, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011; **43**: 1575-1581 [PMID: 21681120 DOI: 10.1249/MSS.0b013e31821ece12]

16 **Bauman A**, Ainsworth BE, Sallis JF, Hagströmer M, Craig CL, Bull FC, Pratt M, Venugopal K, Chau J, Sjöström M. The descriptive epidemiology of sitting. A 20-country comparison using the International Physical Activity Questionnaire (IPAQ). *Am J Prev Med* 2011; **41**: 228-235 [PMID: 21767731 DOI: 10.1016/j.amepre.2011.05.003]

17 **Biswas A**, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med* 2015; **162**: 123-132 [PMID: 25599350 DOI: 10.7326/M14-1651]

18 **Wilmot EG**, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, Khunti K, Yates T, Biddle SJ. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia* 2012; **55**: 2895-2905 [PMID: 22890825 DOI: 10.1007/s00125-012-2677-z]

19 **Hu FB**, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA* 2003; **289**: 1785-1791 [PMID: 12684356 DOI: 10.1001/jama.289.14.1785]

20 **American Diabetes Association**. Standards of Medical Care in Diabetes-2015. *Diabetes Care* 2015; **38**: S1-S93

21 **Pulsford RM**, Stamatakis E, Britton AR, Brunner EJ, Hillsdon M. Associations of sitting behaviours with all-cause mortality over a 16-year follow-up: the Whitehall II study. *Int J Epidemiol* 2015; **44**: 1909-1916 [PMID: 26454871 DOI: 10.1093/ije/dyv191]

22 **Tanasescu M**, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA* 2002; **288**: 1994-2000 [PMID: 12387651 DOI: 10.1001/jama.288.16.1994]

23 **Rafferty AP**, Reeves MJ, McGee HB, Pivarnik JM. Physical activity patterns among walkers and compliance with public health recommendations. *Med Sci Sports Exerc* 2002; **34**: 1255-1261 [PMID: 12165679 DOI: 10.1097/00005768-200208000-00005]

24 **Hays LM**, Clark DO. Correlates of physical activity in a sample of older adults with type 2 diabetes. *Diabetes Care* 1999; **22**: 706-712 [PMID: 10332670 DOI: 10.2337/diacare.22.5.706]

25 **Hu FB**, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE, Manson JE. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *JAMA* 1999; **282**: 1433-1439 [PMID: 10535433 DOI: 10.1001/jama.282.15.1433]

26 **Tanasescu M**, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation* 2003; **107**: 2435-2439 [PMID: 12719277 DOI: 10.1161/01.CIR.0000066906.11109.1F]

27 **Gregg EW**, Gerzoff RB, Caspersen CJ, Williamson DF, Narayan KM. Relationship of walking to mortality among US adults with diabetes. *Arch Intern Med* 2003; **163**: 1440-1447 [PMID: 12824093 DOI: 10.1001/archinte.163.12.1440]

28 **Shephard RJ**. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med* 2003; **37**: 197-206; discussion 206 [PMID: 12782543 DOI: 10.1136/bjsm.37.3.197]

29 **Califf RM**, Boolell M, Haffner SM, Bethel M, McMurray J, Duggal A, Holman RR; NAVIGATOR Study Group. Prevention of diabetes and cardiovascular disease in patients with impaired glucose tolerance: rationale and design of the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial. *Am Heart J* 2008; **156**: 623-632 [PMID: 18946890]

30 **NAVIGATOR Study Group**, Holman RR, Haffner SM, McMurray JJ, Bethel MA, Holzhauer B, Hua TA, Belenkov Y, Boolell M, Buse JB, Buckley BM, Chacra AR, Chiang FT,

Charbonnel B, Chow CC, Davies MJ, Deedwania P, Diem P, Einhorn D, Fonseca V, Fulcher GR, Gaciong Z, Gaztambide S, Giles T, Horton E, Ilkova H, Jenssen T, Kahn SE, Krum H, Laakso M, Leiter LA, Levitt NS, Mareev V, Martinez F, Masson C, Mazzone T, Meaney E, Nesto R, Pan C, Prager R, Raptis SA, Rutten GE, Sandstroem H, Schaper F, Scheen A, Schmitz O, Sinay I, Soska V, Stender S, Tamás G, Tognoni G, Tuomilehto J, Villamil AS, Vozár J, Califf RM. Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010; **362**: 1463-1476 [PMID: 20228402 DOI: 10.1056/NEJMoa1001122]

31 **NAVIGATOR Study Group**, McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA, Belenkov Y, Boolell M, Buse JB, Buckley BM, Chacra AR, Chiang FT, Charbonnel B, Chow CC, Davies MJ, Deedwania P, Diem P, Einhorn D, Fonseca V, Fulcher GR, Gaciong Z, Gaztambide S, Giles T, Horton E, Ilkova H, Jenssen T, Kahn SE, Krum H, Laakso M, Leiter LA, Levitt NS, Mareev V, Martinez F, Masson C, Mazzone T, Meaney E, Nesto R, Pan C, Prager R, Raptis SA, Rutten GE, Sandstroem H, Schaper F, Scheen A, Schmitz O, Sinay I, Soska V, Stender S, Tamás G, Tognoni G, Tuomilehto J, Villamil AS, Vozár J, Califf RM. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010; **362**: 1477-1490 [PMID: 20228403 DOI: 10.1056/NEJMoa1001121]

32 **Yates T**, Haffner SM, Schulte PJ, Thomas L, Huffman KM, Bales CW, Califf RM, Holman RR, McMurray JJ, Bethel MA, Tuomilehto J, Davies MJ, Kraus WE. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. *Lancet* 2014; **383**: 1059-1066 [PMID: 24361242 DOI: 10.1016/S0140-6736(13)62061-9]

33 **Park S**, Park H, Togo F, Watanabe E, Yasunaga A, Yoshiuchi K, Shephard RJ, Aoyagi Y. Year-long physical activity and metabolic syndrome in older Japanese adults: cross-sectional data from the Nakanojo Study. *J Gerontol A Biol Sci Med Sci* 2008; **63**: 1119-1123 [PMID: 18948564 DOI: 10.1093/gerona/63.10.1119]

34 **Knowler WC**, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393-403 [PMID: 11832527 DOI: 10.1056/NEJMoa012512]

35 **Pan XR**, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 1997; **20**: 537-544 [PMID: 9096977 DOI: 10.2337/diacare.20.4.537]

36 **Kosaka K**, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. *Diabetes Res Clin Pract* 2005; **67**: 152-162 [PMID: 15649575 DOI: 10.1016/j.diabres.2004.06.010]

37 **Walker KZ**, Piers LS, Putt RS, Jones JA, O'Dea K. Effects of regular walking on cardiovascular risk factors and body composition in normoglycemic women and women with type 2 diabetes. *Diabetes Care* 1999; **22**: 555-561 [PMID: 10189531 DOI: 10.2337/diacare.22.4.555]

38 **Yamanouchi K**, Shinozaki T, Chikada K, Nishikawa T, Ito K, Shimizu S, Ozawa N, Suzuki Y, Maeno H, Kato K. Daily walking combined with diet therapy is a useful means for obese NIDDM patients not only to reduce body weight but also to improve insulin sensitivity. *Diabetes Care* 1995; **18**: 775-778 [PMID: 7555502 DOI: 10.2337/diacare.18.6.775]

39 **Qiu S**, Cai X, Schumann U, Velders M, Sun Z, Steinacker JM. Impact of walking on glycemic control and other cardiovascular risk factors in type 2 diabetes: a meta-analysis. *PLoS One* 2014; **9**: e109767 [PMID: 25329391 DOI: 10.1371/journal.pone.0109767]

40 **Henson J**, Davies MJ, Bodicoat DH, Edwardson CL, Gill JM, Stensel DJ, Tolfrey K, Dunstan DW, Khunti K, Yates T. Breaking Up Prolonged Sitting With Standing or Walking Attenuates the Postprandial Metabolic Response in Postmenopausal Women: A Randomized Acute Study. *Diabetes Care* 2016; **39**: 130-138 [PMID: 26628415 DOI: 10.2337/dc15-1240]

41 **Karstoft K**, Winding K, Knudsen SH, Nielsen JS, Thomsen C, Pedersen BK, Solomon TP. The effects of free-living interval-walking training on glycemic control, body composition, and physical fitness in type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care* 2013; **36**: 228-236 [PMID: 23002086 DOI: 10.2337/dc12-0658]

42 **Karstoft K**, Christensen CS, Pedersen BK, Solomon TP. The acute effects of interval- Vs continuous-walking exercise on glycemic control in subjects with type 2 diabetes: a crossover, controlled study. *J Clin Endocrinol Metab* 2014; **99**: 3334-3342 [PMID: 24905068 DOI: 10.1210/jc.2014-1837]

43 **Rowinski R**, Dabrowski A, Kostka T. Gardening as the dominant leisure time physical activity (LTPA) of older adults from a post-communist country. The results of the population-based PolSenior Project from Poland. *Arch Gerontol Geriatr* 2015; **60**: 486-491 [PMID: 25661458 DOI: 10.1016/j.archger.2015.01.011]

44 **Mooney SJ**, Joshi S, Cerdá M, Quinn JW, Beard JR, Kennedy GJ, Benjamin EO, Ompad DC, Rundle AG. Patterns of Physical Activity Among Older Adults in New York City: A Latent Class Approach. *Am J Prev Med* 2015; **49**: e13-e22 [PMID: 26091927 DOI: 10.1016/j.amepre.2015.02.015]

45 **Nicklett EJ**, Anderson LA, Yen IH. Gardening Activities and Physical Health Among Older Adults: A Review of the Evidence. *J Appl Gerontol* 2014 Dec 16; Epub ahead of print [PMID: 25515757 DOI: 10.1177/0733464814563608]

46 **Arcury TA**, Snively BM, Bell RA, Smith SL, Stafford JM, Wetmore-Arkader LK, Quandt SA. Physical activity among rural older adults with diabetes. *J Rural Health* 2006; **22**: 164-168 [PMID: 16606429 DOI: 10.1111/j.1748-0361.2006.00026.x]

47 **Cloix L**, Caille A, Helmer C, Bourdel-Marchasson I, Fagot-Campagna A, Fournier C, Lecomte P, Oppert JM, Jacobi D. Physical activity at home, at leisure, during transportation and at work in French adults with type 2 diabetes: the ENTRED physical activity study. *Diabetes Metab* 2015; **41**: 37-44 [PMID: 25277526 DOI: 10.1016/j.diabet.2014.07.003]

48 **Stamatakis E**, Hamer M, Lawlor DA. Physical activity, mortality, and cardiovascular disease: is domestic physical activity beneficial? The Scottish Health Survey -- 1995, 1998, and 2003. *Am J Epidemiol* 2009; **169**: 1191-1200 [PMID: 19329529 DOI: 10.1093/aje/kwp042]

49 **Yu R**, Leung J, Woo J. Housework reduces all-cause and cancer mortality in Chinese men. *PLoS One* 2013; **8**: e61529 [PMID: 23667441 DOI: 10.1371/journal.pone.0061529]

50 **Lawlor DA**, Taylor M, Bedford C, Ebrahim S. Is housework good for health? Levels of physical activity and factors associated with activity in elderly women. Results from the British Women's Heart and Health Study. *J Epidemiol Community Health* 2002; **56**: 473-478 [PMID: 12011209 DOI: 10.1136/jech.56.6.473]

51 **Manini TM**, Everhart JE, Patel KV, Schoeller DA, Colbert LH, Visser M, Tylavsky F, Bauer DC, Goodpaster BH, Harris TB. Daily activity energy expenditure and mortality among older adults. *JAMA* 2006; **296**: 171-179 [PMID: 16835422 DOI: 10.1001/jama.296.2.171]

52 **Beddhu S**, Wei G, Marcus RL, Chonchol M, Greene T. Light-intensity physical activities and mortality in the United States general population and CKD subpopulation. *Clin J Am Soc Nephrol* 2015; **10**: 1145-1153 [PMID: 25931456 DOI: 10.2215/CJN.08410814]

53 **Steeves JA**, Murphy RA, Crainiceanu CM, Zipunnikov V, Van Domelen DR, Harris TB. Daily Patterns of Physical Activity by Type 2 Diabetes Definition: Comparing Diabetes, Prediabetes, and Participants with Normal Glucose Levels in NHANES 2003-2006. *Prev Med Rep* 2015; **2**: 152-157 [PMID: 25909051 DOI: 10.1016/j.pmedr.2015.02.007]

54 **Levine JA**. Non-exercise activity thermogenesis (NEAT). *Nutr Rev* 2004; **62**: S82-S97 [PMID: 15387473 DOI: 10.1111/j.1753-4887.2004.tb00094.x]

55 **Donahoo WT**, Levine JA, Melanson EL. Variability in energy expenditure and its components. *Curr Opin Clin Nutr Metab Care*

2004; **7**: 599-605 [PMID: 15534426 DOI: 10.1097/00075197-200411000-00003]
56 **Levine JA**, Vander Weg MW, Hill JO, Klesges RC. Non-exercise activity thermogenesis: the crouching tiger hidden dragon of societal weight gain. *Arterioscler Thromb Vasc Biol* 2006; **26**: 729-736 [PMID: 16439708 DOI: 10.1161/01.ATV.0000205848.83210.73]
57 **Alahmadi MA**, Hills AP, King NA, Byrne NM. Exercise intensity influences nonexercise activity thermogenesis in overweight and obese adults. *Med Sci Sports Exerc* 2011; **43**: 624-631 [PMID: 21412111 DOI: 10.1249/MSS.0b013e3181f7a0cb]
58 **Levine JA**, McCrady SK, Boyne S, Smith J, Cargill K, Forrester T. Non-exercise physical activity in agricultural and urban people. *Urban Stud* 2011; **48**: 2417-2427 [PMID: 22073428 DOI: 10.1177/0042098010379273]
59 **Levine JA**, McCrady SK, Lanningham-Foster LM, Kane PH, Foster RC, Manohar CU. The role of free-living daily walking in human weight gain and obesity. *Diabetes* 2008; **57**: 548-554 [PMID: 18003759 DOI: 10.2337/db07-0815]
60 **Schmidt SL**, Harmon KA, Sharp TA, Kealey EH, Bessesen DH. The effects of overfeeding on spontaneous physical activity in obesity prone and obesity resistant humans. *Obesity* (Silver Spring) 2012; **20**: 2186-2193 [PMID: 22522883 DOI: 10.1038/oby.2012.103]
61 **Levine JA**, Nygren J, Short KR, Nair KS. Effect of hyperthyroidism on spontaneous physical activity and energy expenditure in rats. *J Appl Physiol* (1985) 2003; **94**: 165-170 [PMID: 12486020]
62 **Levine JA**, Eberhardt NL, Jensen MD. Leptin responses to overfeeding: relationship with body fat and nonexercise activity thermogenesis. *J Clin Endocrinol Metab* 1999; **84**: 2751-2754 [PMID: 10443673 DOI: 10.1210/jc.84.8.2751]
63 **Bowen RS**, Knab AM, Hamilton AT, McCall JR, Moore-Harrison TL, Lightfoot JT. Effects of Supraphysiological Doses of Sex Steroids on Wheel Running Activity in Mice. *J Steroids Horm Sci* 2012; **3**: 110 [PMID: 25419484 DOI: 10.4172/2157-7536.1000110]
64 **Kotz CM**. Integration of feeding and spontaneous physical activity: role for orexin. *Physiol Behav* 2006; **88**: 294-301 [PMID: 16787655]
65 **Garland T**, Schutz H, Chappell MA, Keeney BK, Meek TH, Copes LE, Acosta W, Drenowatz C, Maciel RC, van Dijk G, Kotz CM, Eisenmann JC. The biological control of voluntary exercise, spontaneous physical activity and daily energy expenditure in relation to obesity: human and rodent perspectives. *J Exp Biol* 2011; **214**: 206-229 [PMID: 21177942 DOI: 10.1242/jeb.048397]
66 **Villablanca PA**, Alegria JR, Mookadam F, Holmes DR, Wright RS, Levine JA. Nonexercise activity thermogenesis in obesity management. *Mayo Clin Proc* 2015; **90**: 509-519 [PMID: 25841254 DOI: 10.1016/j.mayocp.2015.02.001]
67 **Look AHEAD Research Group**, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Reboussin D, Regensteiner JG, Rickman AD, Ryan DH, Safford M, Wadden TA, Wagenknecht LE, West DS, Williamson DF, Yanovski SZ. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; **369**: 145-154 [PMID: 23796131 DOI: 10.1056/NEJMoa1212914]
68 **Matthews CE**, Jurj AL, Shu XO, Li HL, Yang G, Li Q, Gao YT, Zheng W. Influence of exercise, walking, cycling, and overall nonexercise physical activity on mortality in Chinese women. *Am J Epidemiol* 2007; **165**: 1343-1350 [PMID: 17478434]
69 **Hagger-Johnson G**, Gow AJ, Burley V, Greenwood D, Cade JE. Sitting Time, Fidgeting, and All-Cause Mortality in the UK Women's Cohort Study. *Am J Prev Med* 2016; **50**: 154-160 [PMID: 26416340 DOI: 10.1016/j.amepre.2015.06.025]
70 **Hamasaki H**, Yanai H, Mishima S, Mineyama T, Yamamoto-Honda R, Kakei M, Ezaki O, Noda M. Correlations of non-exercise activity thermogenesis to metabolic parameters in Japanese patients with type 2 diabetes. *Diabetol Metab Syndr* 2013; **5**: 26 [PMID: 23711224 DOI: 10.1186/1758-5996-5-26]
71 **Hamasaki H**, Noda M, Moriyama S, Yoshikawa R, Katsuyama H, Sako A, Mishima S, Kakei M, Ezaki O, Yanai H. Daily Physical Activity Assessed by a Triaxial Accelerometer Is Beneficially Associated with Waist Circumference, Serum Triglycerides, and Insulin Resistance in Japanese Patients with Prediabetes or Untreated Early Type 2 Diabetes. *J Diabetes Res* 2015; **2015**: 526201 [PMID: 26064983 DOI: 10.1155/2015/526201]
72 **Hamasaki H**, Yanai H, Kakei M, Noda M, Ezaki O. The association between daily physical activity and plasma B-type natriuretic peptide in patients with glucose intolerance: a cross-sectional study. *BMJ Open* 2015; **5**: e006276 [PMID: 25596197 DOI: 10.1136/bmjopen-2014-006276]

P- Reviewer: Panchu P, Tamemoto H, Verrotti A **S- Editor**: Gong XM
L- Editor: A **E- Editor**: Lu YJ

World Journal of Diabetes

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4239/wjd.v7.i12.252

World J Diabetes 2016 June 25; 7(12): 252-259
ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Does parity worsen diabetes-related chronic complications in women with type 1 diabetes?

Marilia Brito Gomes, Carlos Antonio Negrato, Ana Almeida, Antonio Ponce de Leon

Marilia Brito Gomes, Ana Almeida, Department of Internal Medicine, Diabetes Unit, State University of Rio de Janeiro, Rio de Janeiro 20550-900, Brazil

Carlos Antonio Negrato, Bauru's Diabetics Association, Bauru, São Paulo 17012-433, Brazil

Antonio Ponce de Leon, Department of Epidemiology, State University of Rio de Janeiro, Rio de Janeiro 20550-900, Brazil

Author contributions: Gomes MB, Negrato CA, Almeida A and de Leon AP analyzed the data and wrote the manuscript; Almeida A collected the data.

Supported by The Farmanguinhos/Fundação Oswaldo Cruz/National Health Ministry, Brazilian Diabetes Society, Fundação do Amparo à Pesquisa do Estado do Rio de Janeiro, and Conselho Nacional de Desenvolvimento Científico e Tecnológico do Brasil, No. 563753/2010-2.

Institutional review board statement: The study was reviewed and approved by the State University of Rio de Janeiro Institutional Review Board and Bauru's Diabetics Association Institutional Review Board.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: The authors declare that they have no conflict of interests to disclose.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Carlos Antonio Negrato, MD, PhD, Bauru's Diabetics Association, Rua Saint Martin 27-07, Bauru, São Paulo 17012-433, Brazil. carlosnegrato@uol.com.br
Telephone: +55-14-32348915
Fax: +55-14-32348915

Received: December 15, 2015
Peer-review started: December 18, 2015
First decision: February 29, 2016
Revised: March 31, 2016
Accepted: May 7, 2016
Article in press: May 9, 2016
Published online: June 25, 2016

Abstract

AIM: To determine the relationship between parity, glycemic control, cardiovascular risk factors and diabetes-related chronic complications in women with type 1 diabetes.

METHODS: This was a multicenter cross-sectional study conducted between December 2008 and December 2010 in 28 public clinics in 20 cities from the 4 Brazilian geographic regions. Data were obtained from 1532 female patients, 59.2% Caucasians, and aged 25.2 ± 10.6 years. Diabetes duration was of 11.5 ± 8.2 years. Patient's information was obtained through a questionnaire and a chart review. Parity was stratified in five groups: Group 0 (nulliparous), group 1 (1 pregnancy), group 2 (2 pregnancies), group 3 (3 pregnancies), group 4 (≥ 4 pregnancies). Test for trend and multivariate random intercept logistic and linear regression models were used to evaluate the effect of parity upon glycemic control, cardiovascular risk factors and diabetes-related complications.

RESULTS: Parity was not related with glycemic control and nephropathy. Moreover, the effect of parity upon hypertension, retinopathy and macrovascular disease did not persist after adjustments for demographic and

clinical variables in multivariate analysis. For retinopathy, the duration of diabetes and hypertension were the most important independent variables and for macrovascular disease, these variables were age and hypertension. Overweight or obesity was noted in a total of 538 patients (35.1%). A linear association was found between the frequency of overweight or obesity and parity (P = 0.004). Using a random intercept multivariate linear regression model with body mass index (BMI) as dependent variable a borderline effect for parity (P = 0.06) was noted after adjustment for clinical and demographic data. The observed variability of BMI was not attributable to differences between centers.

CONCLUSION: Our results suggest that parity has a borderline effect on body mass index but does not have an important effect upon hypertension and micro or macrovascular chronic complications. Future prospective evaluations must be conducted to clarify the relationship between parity, appearance or worsening of diabetes-related chronic complications.

Key words: Type 1 diabetes; Parity; Glycemic control; Cardiovascular risk factors; Diabetes-related chronic complications

Core tip: To the best of our knowledge, this was the largest study ever conducted with pregnant women with type 1 diabetes in Brazil and maybe in Latin America. Our results suggest that parity did not have an important effect upon hypertension and micro or macrovascular diabetes-related chronic complications. Further prospective studies with a larger number of patients must be addressed to clarify the relationship between parity, appearance or worsening of diabetes-related chronic complications.

Gomes MB, Negrato CA, Almeida A, de Leon AP. Does parity worsen diabetes-related chronic complications in women with type 1 diabetes? *World J Diabetes* 2016; 7(12): 252-259 Available from: URL: http://www.wjgnet.com/1948-9358/full/v7/i12/252.htm DOI: http://dx.doi.org/10.4239/wjd.v7.i12.252

INTRODUCTION

There is a controversy about the impact of pregnancy and parity on the appearance of diabetes-related chronic complications or the progression of its course if they are already present in women with preexisting type 1 diabetes (T1D)[1,2].

Some studies found a worsening of retinopathy during pregnancy[3-5], which was not confirmed by others[2-4,6]. The worsening of retinopathy could be explained by several risk factors such as pregnancy *per se*, hypertension, hyperglycemia, duration of diabetes and a rapid drop in blood glucose levels aiming to reach normoglycemia[5]. Also the presence of increased circulating levels of insulin-like growth factor (IGF-1) that occurs normally during pregnancy could accelerate the progression of an already existing retinopathy[7]. The association between pregnancy and nephropathy is related to an increased albuminuria or alterations on glomerular filtration rate[8]. So far, the mechanisms linking pregnancy to both chronic complications are still unclear and controversial. Some studies showed an association between improvement of glycemic control under intensive insulin therapy and worsening of retinopathy but not nephropathy[5,9].

Other conditions involved in the pathophysiology of diabetes-related chronic complications must be addressed such as pre-pregnancy body mass index (BMI) and blood pressure levels, which have been increasing in the last three decades in some populations[10]. In a Swedish study, it was found that the combination of T1D and overweight/obesity confers a high risk for adverse outcomes, like pre-eclampsia, that increases proportionally to BMI[11]. Otherwise, when women with T1D presenting the features of metabolic syndrome become pregnant, they generally have the coexistence of vascular complications[12]. It has also been shown that women with T1D and pre-eclampsia or pregnancy-induced hypertension present high risk of severe retinopathy later in life[13].

In the Eurodiab study a better glycemic control was found among parous women than nulliparous, and parity did not influence the levels of microalbuminuria and preexisting retinopathy[14]. In a Finnish study it was found a slower progression of retinopathy in parous women than in nulliparous[15].

Considering the scarcity of data regarding the relationship between parity, glycemic control and diabetes-related chronic complications in women with T1D in Brazil, the Brazilian Type 1 Diabetes Study Group (BrazDiab1SG) conducted this survey aiming to analyze the impact of parity in the above mentioned clinical conditions.

MATERIALS AND METHODS

Patients and methods

This was a multicenter, cross-sectional, observational study conducted between December 2008 and December 2010 in 28 public secondary and tertiary care-level clinics from the National Brazilian Health Care System, located in 20 cities in all Brazilian geographic regions (North/Northeast, Mid-West, Southeast, and South). The details of the data collection methods have been published previously[16]. Two thousand and ten patients, 56% female (2010, 56% female) patients that were diagnosed between 1960 and 2010 were included in the study. Among the 2010 enrolled women, only those who knew their age at menarche were included (n = 1532, 76.2%). Patients who did not have had menarche (n = 467, 23.2%) and women with incomplete information for parity (n = 11, 0.5%) were excluded.

Each local ethics committees approved the study (Appendix 1). All patients or their parents, when necessary, signed a written informed consent agreeing

with their participation in the study.

During a clinical visit, a questionnaire was applied in order to collect demographic, educational and economic data. The following variables were assessed then: Age, age at diagnosis, duration of diabetes, height (m), weight (kg), blood pressure, parity, comorbidities, smoking status and the use of metformin.

Data from the last clinical visit were obtained from medical records such as levels of glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Diabetes-related chronic complications were screened in all patients with diabetes duration longer than 5 years, such as retinopathy (by fundoscopy; classified as absent, non-proliferative or proliferative), clinical nephropathy [according to American Diabetes Association (ADA)] recommendations[17], macrovascular diseases (clinical coronary artery disease, stroke, and peripheral vascular disease), and foot alterations. The following goals for adequate metabolic control that are adopted by the ADA[17] were also adopted by the BrazDiab1SG: HbA1c at goal was defined as HbA1c levels of < 58 mmol/mol (7.5%) for patients with T1D between 13 and 19 years old; < 64 mmol/mol (8%) for patients between 6 and 12 years old; between 58 mmol/mol (7.5%) and 69 mmol/mol (8.5%) for patients < 6 years old; and < 53 mmol/mol (7%) for adult patients[17]. Poor glycemic control was considered as having HbA1c levels higher than 75 mmol/mol (9%).

Hypertension was defined as a systolic blood pressure (sBP) $\geqslant$ 140 mmHg and/or diastolic blood pressure (dBP) $\geqslant$ 90 mmHg, use of antihypertensive agents or self-reported for adults; in adolescents hypertension was defined as a sBP or dBP $\geqslant$ 95th percentile for age, sex and height[17].

Overweight was defined as a BMI $\geqslant$ 25 kg/m^2, and obesity as a BMI $\geqslant$ 30 kg/m^2 in adults[18]. Overweight was considered as a BMI of $\geqslant$ 85th percentile for age and gender, and obesity as a BMI of $\geqslant$ 95th percentile for age and gender for adolescents[18].

In 1347 patients (88.0%), HbA1c was measured using methods certified by the National Glycohemoglobin Standardization Program (NGSP): High-performance liquid chromatography in 733 patients (54.3%) and turbidimetry in 614 patients (45.7%). Measurement of HbA1c levels using methods that were not certified by the NGSP and patients with no data on HbA1c levels or use of methodology not certified by the NGSP were not included in the analyses of glycemic control (n = 185, 12.0%). Enzymatic techniques were used to measure FPG, triglycerides, HDL cholesterol, and total cholesterol. Friedewald's equation was used to calculate LDL cholesterol[19]. Patients smoking more than one cigarette per day at the time of the interview were considered as current smokers.

Sample calculation and economic status

The study sample calculation was done according to a methodology described elsewhere[16]. Our sample represented the distribution of T1D cases all over Brazil that was estimated using the overall population distribution reported in the 2000 Brazilian Institute of Geography and Statistics Population Census (IBGE)[20]. These data were combined with national estimates of diabetes prevalence determined by a survey conducted in 1988 in order to determine the minimum number of patients that should be studied in each geographic region of the country[21]. Economic status was defined according to the Brazilian Economic Classification Criteria[22]. This classification also takes in account the education level: Illiterate/incomplete primary education, complete primary education/incomplete secondary education, complete secondary education/incomplete high school, complete high school/some college or college graduate. The following economic status categories were considered: High, middle, low, and very low[22].

Statistical analysis

The data were summarized as means (± SD) and median (minimum-maximum) for continuous variables and as counts (relative frequencies) for discrete variables. Patients were stratified in five groups according to parity: Group 0 (nulliparous), group 1 (1 pregnancy), group 2 (2 pregnancies), group 3 (3 pregnancies) and group 4 ($\geqslant$ 4 pregnancies).

ANOVA test with Sidak correction was used. Test for trend (linear association) was used to analyze the association between parity and frequency of retinopathy, albuminuria and hypertension. A multivariate random intercept logistic regression model was performed with retinopathy (yes/no) as the dependent (outcome) variable and parity as the independent (exposure) variable. Other independent variables, such as socioeconomic status, ethnicity (Caucasian or non-Caucasian based on self-reporting), age, duration of diabetes, HbA1c levels and hypertension (yes/no) were also controlled in the analysis. The same multivariate model was performed with the following dependent variables: Hypertension (yes/no), adding to the set of independent variables, creatinine levels, BMI and smoking status and excluding hypertension; macrovascular disease with the same demographic variables above-mentioned as independent variables adding to the model: Hypertension (yes/no), HbA1c and LDL-Cholesterol levels and smoking status (yes/no). A random intercept multivariate linear regression model was further applied to BMI as dependent variable (three nested models were considered). All analyses were performed using the SPSS version 17.0, SPSS, Inc., Chicago, Illinois, United States, except the random intercept models that were fitted using MLwiN[23]. Odds ratios (ORs) with 95%CIs, variance and standard error

Table 1 Clinical and demographic data of the studied population

Variable	
n	1532
Age, yr	25.2 ± 10.6
Age at diabetes diagnosis, yr	11.4 ± 8.1
Age at menarche, yr	12.7 ± 1.7
Duration of diabetes, yr	11.5 ± 8.2
Ethnicity, *n* (%)[1]	
Caucasian	907 (59.2)
Non-caucasian[1]	625 (40.7)
Geographic region, *n* (%)	
Southeast	611 (39.9)
North/Northeast	454 (29.6)
South	367 (24.0)
Mid-west	100 (6.5)
Economic status	
High	104 (6.7)
Medium	383 (25.0)
Low	533 (34.8)
Very low	512 (33.4)
Level of care, *n* (%)	
Secondary	412 (26.9)
Tertiary	1117 (73.1)
Time of follow-up, yr	7.1 (< 1 to 49)

Data are presented as number (percentage), mean ± SD or median (minimum/maximum). [1]African-Brazilians, Mulattos, Asians, and Native Indians.

were calculated when indicated. A two-sided *P* value less than 0.05 was considered significant.

The statistical review of the study was performed by a biomedical statistician that is also a co-author (APL).

RESULTS

Overview of the studied population

Data were obtained from 1532 patients (excluded *n* = 478, 23.7%). The economic status of 1045 (68.2%) of the patients was either very low or low. Table 1 lists the demographic data of the studied population.

Overview of the studied population stratified according to parity, demographics and socioeconomic status data

The comparison between the patients stratified according to parity showed that patients from groups 0, 1 and 2 were younger than patients from group 4 ($P < 0.001$). Patients from groups 0 and 1 had been diagnosed with diabetes with lower age and had less duration of diabetes than patients from the other groups ($P < 0.001$). A difference between the five groups and geographic regions of the country was observed, being the difference accounted by Mid-West region, that had no patients in group four. These data are described in Table 2.

Overview of the studied population stratified according to parity, glycemic and cardiovascular risk factors control

Overweight or obesity was noted in 538 patients (35.1%). Patients from group 0 had lower BMI than patients from the other groups. A linear association was found between the frequency of overweight or obesity and parity ($P = 0.004$). Using a random intercept multivariate linear regression model with BMI as dependent variable a borderline effect for parity ($P = 0.06$) was noted after adjustment for clinical and demographic data (model 2 and model 3). The significant effect of low insulin dose and age persisted. The observed variability of BMI was not attributable to centers. These data are described in Table 3.

A lower level of HbA1c was found in patients from group 2 in comparison to patients from group 0. No differences between the five groups were observed for the number of patients reaching the target of HbA1c. A higher frequency of hypertension and higher levels of sBP and dBP were observed in group 4 in comparison to the other groups ($P < 0.01$ for all comparisons).

A higher HDL-cholesterol was observed in group 4 in comparison to the other groups. No other difference in lipid parameters was noted. Metformin was used by 162 (10.6 %) patients, and its use was related to parity ($P = 0.02$). The use of metformin was more frequently found in patients from group 4 in comparison with patients from groups 0, 1 and 3, respectively 9 (17.3%) *vs* 103 (10.2%) *vs* 20 (8.4) *vs* 7 (7.4), $P = 0.04$. A higher insulin dose/kg was used by patients from group 0 in comparison to patients from the other groups. The demographic, clinical, and laboratory data of patients stratified by parity are described in Table 2.

Overview of the studied population stratified according to parity and diabetes-related chronic complications

Overall, 1219 (79.7%) of the patients had criteria to be screened for diabetes-related chronic complications. Parity was related to the presence of diabetes-related chronic complications both micro and macrovascular. Considering women with information regarding retinopathy, ($n = 1033$, 84.7%) a lower frequency of non-proliferative and proliferative retinopathy was noted in patients from group 0 in comparison to the other groups ($P < 0.01$). A tendency for an association between parity and nephropathy was observed ($P = 0.08$) in those patients with information obtained in the previous year ($n = 1041$, 85.4%). These data are shown in Table 2.

Using a multivariate random intercept logistic regression model with retinopathy as the dependent variable no effect of parity was noted but the OR for duration of diabetes and presence of hypertension were 1.11 (95%CI: 1.08-1.14, $P < 0.001$) and 3.51 (95%CI: 2.42-5.08, $P < 0.001$), respectively. The other independent variables did not reach statistical significance. The same model with macrovascular disease as dependent variable also showed no effect of parity but the OR for age was 1.067 (95%CI: 1.03-1.106, $P < 0.0001$), while for HbA1c levels it was 1.166 (95%CI: 1.023-1.330, $P < 0.02$) and for hypertension it was 2.29 (95%CI: 1.219-4.306, $P < 0.02$). The other independent variables did not reach statistical significance.

In multivariate random intercept logistic regression

Table 2 Clinical, demographic and laboratory data stratified by parity

Variable	Parity					
	Group 0 (nulliparous)	Group 1 (1 pregnancy)	Group 2 (2 pregnancies)	Group 3 (3 pregnancies)	Group 4 (⩾ 4 pregnancies)	[1]*P*-value
n (%)	1014 (66.2)	238 (15.5)	147 (9.6)	81 (5.3)	52 (3.4)	
Demographic and economic status data						
Age, yr	20.7 ± 7.9	30.2 ± 8.5	34.6 ± 8.6	38.4 ± 9.6	42.3 ± 10.7	< 0.001
< 15	191 (18.7)	1 (0.4)	0	0	0	
15-30	706 (69.6)	117 (49.2)	42 (28.6)	12 (14.8)	6 (11.5)	
⩾ 30	117 (11.5)	120 (50.4)	105 (71.4)	69 (85.2)	46 (88.5)	
Duration of DM, yr	9.4 ± 6.9	13.9 ± 8.2	15.3 ± 8.9	17.9 ± 8.9	19.0 ± 10.7	< 0.001
Age at diagnosis, yr	11.2 ± 6.4	16.2 ± 8.4	19.2 ± 8.1	20.5 ± 9.3	23.3 ± 8.8	< 0.001
Ethnicity, yr (%) ⩾[2]						0.7
Caucasian	606 (59.8)	144 (60.5)	83 (56.5)	47 (58.0)	27 (51.9)	
Non-caucasian	408 (40.2)	94 (39.5)	64 (43.5)	34 (42.0)	25 (48.1)	
Geographic region, *n*						0.001
Southeast	410 (40.4)	94 (39.5)	54 (36.7)	31 (38.3)	22 (42.3)	
South	248 (24.5)	53 (22.3)	36 (24.5)	18 (22.2)	12 (23.1)	
North/Northeast	309 (30.5)	69 (29.0)	39 (26.5)	19 (23.5)	18 (34.6)	
Mid-West	47 (4.6)	22 (9.2)	18 (12.2)	13 (16.0)	0	
Economic status (%)						0.5
High	72 (7.1)	16 (6.7)	8 (5.4)	5 (6.2)	3 (5.8)	
Medium	273 (26.9)	56 (23.5)	29 (19.7)	18 (22.2)	7 (13.5)	
Low	340 (33.5)	85 (35.7)	55 (37.4)	33 (40.7)	20 (38.5)	
Very low	329 (32.4)	81 (34.0)	55 (37.4)	25 (30.9)	22 (42.3)	
Glycemic control and insulin dose						
HbA1c (%)	9.6 ± 2.6	9.4 ± 2.4	8.8 ± 2.0	9.4 ± 2.4	9.5 ± 2.0	0.02
HbA1c (mmol/mol)	81.9 ± 28.4	79.9 ± 26.3	73.4 ± 22.2	79.5 ± 26.8	80.4 ± 21.7	
HbA1c (good) *n* (%)	107 (11.9)	21 (10.3)	19 (14.6)	8 (11.3)	3 (6.5)	0.1
H1Ac (poor) *n* (%)	480 (53.5)	99 (48.8)	51 (39.2)	37 (52.1)	27 (58.7)	
Insulin dose (U/kg per day)	0.98 ± 0.4	0.8 ± 0.3	0.8 ± 0.3	0.7 ± 0.4	0.8 ± 0.4	0.001
Metformin use, yr (%)	103 (10.2)	20 (8.4)	24 (16.3)	6 (7.4)	9 (17.3)	0.04
Cardiovascular risk factors						
sBP (mmHg)	110.8 ± 14.6	117.5 ± 15.7	119.6 ± 18.7	119.8 ± 18.9	124.0 ± 21.4	< 0.001
dBP (mmHg)	72.3 ± 10.1	75.2 ± 11.3	74.9 ± 11.5	75.9 ± 11.5	75.9 ± 10.2	< 0.001
Hypertension, yr (%)	158 (16.6)	76 (32.2)	53 (36.3)	29 (35.8)	25 (48.1)	< 0.001
Cholesterol (mg/dL)	176.9 ± 43.7	186.4 ± 43.4	181.3 ± 41.6	182.3 ± 42.0	183.5 ± 44.5	0.055
Triglycerides (mg/dL)	98.7.4 ± 75.0	102.0 ± 61.1	103.2 ± 64.4	116.2 ± 110.6	105.8 ± 94.9	0.3
HDL cholesterol (mg/dL)	54.1 ± 14.4	58.3 ± 18.4	55.2 ± 15.8	55.3 ± 15.3	61.5 ± 17.4	0.01
Non-LDL cholesterol (mg/dL)	122.5 ± 42.6	128.2 ± 39.9	126.0 ± 41.0	124.9 ± 41.2	122.8 ± 43.4	0.5
LDL cholesterol	103.8 ± 34.7	107.6 ± 35.5	105.5 ± 36.5	103.1 ± 31.2	103.3 ± 37.6	0.7
BMI (kg/m^2)	22.8 ± 3.4	23.9 ± 3.8	24.3 ± 3.5	24.4 ± 5.1	25.5 ± 4.6	< 0.001
Overweight or obesity, *n* (%)[1]	338 (33.5)	153 (35.2)	56 (38.1)	36 (44.4)	25 (49.0)	0.004
Retinopathy, yr (%)[3]						< 0.001
Absent	649 (86.9)	154 (73.3)	104 (77)	60 (76.5)	32 (65.3)	
Non-proliferative	50 (6.7)	36 (17.1)	15 (11.1)	11 (14.1)	10 (20.4)	
Proliferative	48 (6.4)	20 (9.5)	16 (11.9)	7 (9.0)	7 (14 .3)	
Nephropathy, yr (%)[4]						0.08
Absent	527 (70.7)	128 (60.7)	91 (67.4)	49 (62.8)	30 (61.2)	
Microalbuminuria	90 (12.1)	43 (20.4)	17 (12.6)	12 (18.8)	8 (28.0)	
Clinical nephropathy	23 (3.1)	9 (4.3)	8 (5.9)	3 (4.7)	2 (5.0)	
Macrovascular complications, yes (%)[5,6]	23 (3.1)	16 (7.6)	13 (9.6)	5 (6.4)	7 (14.3)	< 0.001

[1]The *P* value is related to the comparison among all groups (ANOVA); [2]African-Brazilians, Mulattos, Asians, Native Indians; [3,4,5]Retinopathy, nephropathy and macrovascular complications were considered in patients with criterion to be screened (duration of diabetes ⩾ 5 years, *n* = 1219); [6]Overweight or obesity were considered together. The data are presented as *n* (%) mean ± SD or median (minimum/maximum). HbA1c: Glycated hemoglobin; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; BMI: Body mass index.

model with hypertension as the dependent variable the OR for age was 1.041 (95%CI: 1.021-1.061, $P < 0.001$) for duration of diabetes was 1.031 (95%CI: 1.012-1.056, $P < 0.005$), for BMI was 1.069 (95%CI: 1.029-1.110, $P = 0.005$), and for plasma creatinine level was 2.280 (95%CI: 1.722-3.017, $P < 0.001$). The other independent variables did not reach statistical significance.

A small variability attributable to centers was noted only for macrovascular disease with a variance and standard error of 0.376 (0.276).

DISCUSSION

Our study showed an association between parity with retinopathy, macrovascular disease and hypertension that disappeared after adjustment for variables that

Table 3 Effect of parity on body mass index evaluated by random intercept multivariate linear regression and adjusted for clinical and demographic data

Variable	Model 1	Model 2	Model 3	*P* value
Parity				
Nulliparous (reference)				
1	0.400 (0.278)	0.291 (0.276)	0.291 (0.277)	NS
2	0.366 (0.350)	0.320 (0.347)	0.326 (0.350)	NS
3	0.171 (0.456)	0.119 (0.453)	0.111 (0.454)	NS
⩾ 4	1.013 (0.563)	1.029 (0.558)	1.051 (0.560)	0.06
Age	0.081 (0.014)	0.069 (0.014)	0.069 (0.014)	NS
Duration of diabetes (yr)	0.007 (0.015)	0.011 (0.015)	0.013 (0.015)	NS
Insulin dose (U/kg per day)		-1.237 (0.253)	-1.239 (0.254)	(< 0.001)
Metformin use (yr)		-0.960 (0.678)	-0.994(0.679)	NS
Economic status (classes)				NS
High (reference)				
Medium			0.677 (0.392)	
Low			0.551 (0.386)	
Very low			0.353 (0.397)	
Ethnicity (non-caucasian)			-0.028 (0.201)	NS
Intercept	23.233 (0.166)	23.281 (0.171)	23.814 (0.377)	
Variability attributable to centers				
Variance	0.296 (0.148)	0.340 (0.161)	0.321 (0.155)	
Variability attributable to patients				
Variance	12.475 (0.456)	12.251 (0.448)	12.226 (0.447)	
-2 × loglik	8.192.640	8167.357	8.163.366	

Data are presented as B coefficient or variance (standard error); continuous independent variables are centered on the mean. Model 1: Adjusted for age and duration of diabetes; Model 2: Adjusted for age, duration of diabetes, insulin dose and metformin use; Model 3: Adjusted for age, duration of diabetes, insulin dose, metformin use, economic status and ethnicity. NS: Not significant.

could influence these outcomes, such as age, duration of diabetes, plasma creatinine levels, HbA1c, daily insulin dose and use of metformin. However a borderline effect of parity upon BMI was observed.

The impact of pregnancy and parity on the appearance of diabetes-related chronic complications or the progression of its course is still a matter of controversy[2]. Some studies have found no difference in the prevalence of diabetes-related chronic complications between nulliparous and parous women[24], less progression of retinopathy in multiparous than in nulliparous women[15] and even a limitations of the progression of nephropathy and retinopathy probably due to a better glycemic control found in parous women compared to nulliparous women[14].

An unexpected finding was that a lower daily insulin dose was associated with a higher BMI. The use of metformin had no effect on BMI probably because the majority of women with increased BMI were under the use of metformin; the use of metformin in patients with T1D has not its clear benefits well established but a decrease in insulin daily dose has generally been described[25].

Nevertheless, it is important to emphasize that the absence of data on body weight before each pregnancy and consequently the weight gain during each pregnancy does not allow us to take any conclusions about this relationship. However, recently a study[26] has shown that around 20% of T1D patients have been diagnosed with overweight/obesity. Although weight before the diagnosis of diabetes was not recorded in our sample, more than one-third of the nulliparous women had overweight or obesity. Overweight and obesity are related to insulin resistance which is strongly associated with cardiovascular disease[27]. We have found no effect of parity on cardiovascular disease in our study.

Considering microvascular complications, retinopathy was the most prevalent diabetes-related chronic complication associated with parity but after adjustments for other clinical and demographic variables this association did not show to be significant. Indeed, the most significant variables related to retinopathy were duration of diabetes and the presence of hypertension. The majority of the studies relating pregnancy with retinopathy were prospective and the results were controversial[1,3,4]. The DCCT[1] and the Eurodiab[14] compared women with incident pregnancies during the study period with women who did not conceive. The DCCT study showed a transient worsening of retinopathy, which disappeared 12 mo post-partum and the Eurodiab study did not find any relationship between retinopathy and pregnancy. Indeed, in the Eurodiab study[14] the duration of diabetes and the level of HbA1c were the most important predictors of the occurrence of retinopathy. Two other recent studies showed that progression of sight-threatening retinopathy during pregnancy some years post-partum was related to duration of diabetes, to the presence of macular edema and higher blood pressure levels during pregnancy but not to HbA1c levels[13,28]. Rosenn *et al*[29] performed a large retrospective study with 776 nulliparous women and 582 parous women with T1D and have found an inverse association with parity and the presence of retinopathy.

Considering nephropathy, our data is in accordance with the findings of Reece *et al*[8] that conducted a study with 31 pregnancies complicated by nephropathy and have found a significant increase in maternal blood pressure, proteinuria and nephrotic syndrome in 71% of pregnancies but no adverse effects of pregnancy on the natural course of the underlying renal disease. Miodovnik *et al*[30] have followed a group of 182 pregnant women with T1D, with and without nephropathy. They have found that pregnancy does not increase the risk of nephropathy and does not accelerate its progression.

These studies regarding the progression of retinopathy and nephropathy were prospective. So, our results must then be interpreted with caution due to its cross-sectional design, that does not allow us to deny a causal relationship between parity and occurrence/worsening of retinopathy and nephropathy in our population. Nevertheless, many women had already retinopathy and nephropathy and also important risk factors for the development or progression of both complications such as the presence of overweight or obesity, hypertension, as described in other studies[8,10-13,29,30].

We should also take in account that for hypertension parity did not reach statistical significance in multivariate analysis. Indeed, age, duration of diabetes BMI, ethnicity (Caucasian) and plasma creatinine levels were the most important factors.

The main strength of our large sample size is that it represents the diverse, young Brazilian population with T1D, with a multi-ethnic and different socioeconomic backgrounds. Also a uniform, standardized recruitment protocol in all participating centers was used.

Finally, some limitations must be addressed in our study. The mean age of our patients is around 25 years, which could represent a short time frame to the appearance of diabetes-related chronic complications. Additionally, we do not have data about how long patients had the diagnosis of diabetes at the time of each pregnancy, occurrence of stillbirth, prematurity, neonatal mortality and no information concerning screening for retinopathy and nephropathy during pregnancies.

In conclusion, our data did not find an effect of parity upon diabetes-related chronic complications and hypertension, but a borderline effect on BMI. These findings should allow us not to discourage women without severe and progressive diabetes-related complications to become pregnant if they reach and maintain a good glycemic control. Further prospective studies must be addressed to clarify the mechanisms underlying the relationship between parity, and the appearance or worsening of diabetes comorbidities and the effect of parity on diabetes-related chronic complications.

ACKNOWLEDGMENTS

We thank Ms. Karianne Aroeira Davidson, Mrs. Anna Maria Ferreira from Brazilian Diabetes Society, and Mrs. Elisangela Santos from State University of Rio de Janeiro for their technical assistance.

COMMENTS

Background

It is generally believed that pregnancy itself or an increasing number of pregnancies might worsen diabetes-related chronic complications.

Research frontiers

So far, the mechanisms linking pregnancy to both chronic complications are still unclear and controversial.

Innovations and breakthroughs

For a long time women with diabetes have been discouraged to become pregnant regarding the possibility that an already existing complication might worsen and new complications might appear during pregnancy. This study has shown no relationship between higher parity and the worsening or appearance of diabetes-related chronic complications.

Applications

This study showed an association between parity with retinopathy, macrovascular disease and hypertension that disappeared after adjustment for variables that could influence these outcomes, such as age, duration of diabetes, plasma creatinine levels, HbA1c, daily insulin dose and use of metformin.

Peer-review

The manuscript is well written, and the study results and evaluation means are well defined in detail. It provides additional information on a controversial area, while suitably mentioning the shortcomings of the study as well. It will be of good concern to clinicians/researchers working on this subject, while further research will still be needed for clarification of the mentioned links, as the authors also mention.

REFERENCES

1 **The Diabetes Control and Complications Trial Research Group**. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *Diabetes Care* 2000; **23**: 1084-1091 [PMID: 10937502 DOI: 10.2337/diacare.23.8.1084]

2 **Vääräsmäki M**, Anttila M, Pirttiaho H, Hartikainen AL. Are recurrent pregnancies a risk in Type 1 diabetes? *Acta Obstet Gynecol Scand* 2002; **81**: 1110-1115 [PMID: 12519106 DOI: 10.1034/j.1600-0412.2002.811203.x]

3 **Serup L**. Influence of pregnancy on diabetic retinopathy. *Acta Endocrinol Suppl* (Copenh) 1986; **277**: 122-124 [PMID: 3464145 DOI: 10.1530/acta.0.111s0122]

4 **Horvat M**, Maclean H, Goldberg L, Crock GW. Diabetic retinopathy in pregnancy: a 12-year prospective survey. *Br J Ophthalmol* 1980; **64**: 398-403 [PMID: 7387964 DOI: 10.1136/bjo.64.6.398]

5 **Jovanovic-Peterson L**, Peterson CM. Diabetic retinopathy. *Clin Obstet Gynecol* 1991; **34**: 516-525 [PMID: 1934703 DOI: 10.1097/00003081-199134030-00005]

6 **Lapolla A**, Cardone C, Negrin P, Midena E, Marini S, Gardellin C, Bruttomesso D, Fedele D. Pregnancy does not induce or worsen retinal and peripheral nerve dysfunction in insulin-dependent diabetic women. *J Diabetes Complications* 1998; **12**: 74-80 [PMID: 9559484 DOI: 10.1016/S1056-8727(97)00002-0]

7 **Ringholm L**, Vestgaard M, Laugesen CS, Juul A, Damm P, Mathiesen ER. Pregnancy-induced increase in circulating IGF-I is associated with progression of diabetic retinopathy in women with type 1 diabetes. *Growth Horm IGF Res* 2011; **21**: 25-30 [PMID: 21212010 DOI: 10.1016/j.ghir.2010.12.001]

8 **Reece EA**, Coustan DR, Hayslett JP, Holford T, Coulehan J, O'Connor TZ, Hobbins JC. Diabetic nephropathy: pregnancy performance and fetomaternal outcome. *Am J Obstet Gynecol* 1988; **159**: 56-66 [PMID: 3394754 DOI: 10.1016/0002-9378(88)90494-2]

9 **Dahl-Jørgensen K**, Brinchmann-Hansen O, Hanssen KF, Sandvik

L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. *Br Med J* (Clin Res Ed*)* 1985; **290**: 811-815 [PMID: 3919804 DOI: 10.1136/bmj.290.6471.811]

10 **Klemetti MM**, Teramo K, Nuutila M, Tikkanen M, Hiilesmaa V, Laivuori H. Blood pressure levels but not hypertensive complications have increased in Type 1 diabetes pregnancies during 1989-2010. *Diabet Med* 2013; **30**: 1087-1093 [PMID: 23659525 DOI: 10.1111/dme.12224]

11 **Persson M**, Pasupathy D, Hanson U, Westgren M, Norman M. Pre-pregnancy body mass index and the risk of adverse outcome in type 1 diabetic pregnancies: a population-based cohort study. *BMJ Open* 2012; **2**: e000601 [PMID: 22334581 DOI: 10.1136/bmjopen-2011-000601]

12 **Wender-Ozegowska E**, Zawiejska A, Michalowska-Wender G, Iciek R, Wender M, Brazert J. Metabolic syndrome in type 1 diabetes mellitus. Does it have any impact on the course of pregnancy? *J Physiol Pharmacol* 2011; **62**: 567-573 [PMID: 22204805]

13 **Gordin D**, Kaaja R, Forsblom C, Hiilesmaa V, Teramo K, Groop PH. Pre-eclampsia and pregnancy-induced hypertension are associated with severe diabetic retinopathy in type 1 diabetes later in life. *Acta Diabetol* 2013; **50**: 781-787 [PMID: 22955518 DOI: 10.1007/s00592-012-0415-0]

14 **Chaturvedi N**, Stephenson JM, Fuller JH. The relationship between pregnancy and long-term maternal complications in the EURODIAB IDDM Complications Study. *Diabet Med* 1995; **12**: 494-499 [PMID: 7648822 DOI: 10.1111/j.1464-5491.1995.tb00530.x]

15 **Kaaja R**, Sjöberg L, Hellsted T, Immonen I, Sane T, Teramo K. Long-term effects of pregnancy on diabetic complications. *Diabet Med* 1996; **13**: 165-169 [PMID: 8641123 DOI: 10.1002/(SICI)1096-9136(199602)13:2<165::AID-DIA61>3.0.CO;2-E]

16 **Gomes MB**, Coral M, Cobas RA, Dib SA, Canani LH, Nery M, de Freitas MC, Faria M, Felício JS, da Silva SC, Pedrosa H, Costa e Forti A, Rea RR, Pires AC, Montenegro Junior R, Oliveira JE, Rassi N, Negrato CA. Prevalence of adults with type 1 diabetes who meet the goals of care in daily clinical practice: a nationwide multicenter study in Brazil. *Diabetes Res Clin Pract* 2012; **97**: 63-70 [PMID: 22397904 DOI: 10.1016/j.diabres.2012.02.008]

17 **American Diabetes Association**. Clinical Practice Recommendations. *Diabetes Care* 2013; **34**: S11-S66

18 **World Health Organization**. Obesity: preventing and managing the global epidemic. Report of a World Health Organization Consultation. Geneva: World Health Organization, WHO Obesity Technical Report Series, 2000: 284

19 **Friedewald WT**, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499-502 [PMID: 4337382]

20 **Instituto Brasileiro de Geografia e Estatística (IBGE)**. Censo 2000. [accessed 2008 Aug]. Available from: URL: http://www.ibge.gov.br/censo/

21 **Malerbi DA**, Franco LJ. Multicenter study of the prevalence of diabetes mellitus and impaired glucose tolerance in the urban Brazilian population aged 30-69 yr. The Brazilian Cooperative Group on the Study of Diabetes Prevalence. *Diabetes Care* 1992; **15**: 1509-1516 [PMID: 1468278 DOI: 10.2337/diacare.15.11.1509]

22 **ABEP**. Brazilian Economic classification criteria, 2010. [accessed 2008 Aug]. Available from: URL: http: //www.abep.org/novo/Content.aspx?SectionID=84

23 **Rasbash J**, Charlton C, Browne WJ , Healy M, Cameron B. 2009 MLwiN Version 2.1. Bristol: Centre for Multilevel Modelling, University of Bristol, 2009

24 **Hemachandra A**, Ellis D, Lloyd CE, Orchard TJ. The influence of pregnancy on IDDM complications. *Diabetes Care* 1995; **18**: 950-954 [PMID: 7555555 DOI: 10.2337/diacare.18.7.950]

25 **Vella S**, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR. The use of metformin in type 1 diabetes: a systematic review of efficacy. *Diabetologia* 2010; **53**: 809-820 [PMID: 20057994 DOI: 10.1007/s00125-009-1636-9]

26 **Newfield RS**, Cohen D, Capparelli EV, Shragg P. Rapid weight gain in children soon after diagnosis of type 1 diabetes: is there room for concern? *Pediatr Diabetes* 2009; **10**: 310-315 [PMID: 19067888 DOI: 10.1111/j.1399-5448.2008.00475.x]

27 **Matheus AS**, Tibiriçá E, da Silva PB, de Fátima Bevilácqua da Matta M, Gomes MB. Uric acid levels are associated with microvascular endothelial dysfunction in patients with Type 1 diabetes. *Diabet Med* 2011; **28**: 1188-1193 [PMID: 21658123 DOI: 10.1111/j.1464-5491.2011.03349.x]

28 **Vestgaard M**, Ringholm L, Laugesen CS, Rasmussen KL, Damm P, Mathiesen ER. Pregnancy-induced sight-threatening diabetic retinopathy in women with Type 1 diabetes. *Diabet Med* 2010; **27**: 431-435 [PMID: 20536515 DOI: 10.1111/j.1464-5491.2010.02958.x]

29 **Rosenn BM**, Miodovinik M. Pregnancy and complications of diabetes mellitus: maternal and fetal complications, edn 2. In Diabetes mellitus: A Fundamental and clinical Text. Philadelphia, PA: Lippincott, Williams, and Wilkins, 2000: 865-866

30 **Miodovnik M**, Rosenn BM, Khoury JC, Grigsby JL, Siddiqi TA. Does pregnancy increase the risk for development and progression of diabetic nephropathy? *Am J Obstet Gynecol* 1996; **174**: 1180-1189; discussion 1189-1191 [PMID: 8623845 DOI: 10.1016/S0002-9378(96)70660-9]

P- Reviewer: Sanlioglu AD, Vorobjova T **S- Editor**: Kong JX
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com