EDORIUM Journals

Edorium J Pathol 2015;2:5–9.
www.edoriumjournalofpathology.com

EDITORIAL OPEN ACCESS

The research on vitamin D and cancer in Italy. Searching for an authorative expertise: The case of the University of Verona

Salvatore Chirumbolo

A recent animated discussion within the research group where I was working suggested for the existence of a great concern about who and how may be the principal expert in the field, an expert able to fulfill the expectation coming from the most common people whether really vitamin D supplementation exerts wondrous properties on human health or not. Table 1 summarizes how many fundamental research teams are endeavoured with vitamin D in the medical field within the University where I am working. This overview should shed a light on how this topic is inflated in medical science, even offering a limited example such this. Therefore, this may suggest that experts in the field about vitamin D are really biochemists, physicians or other graduated and postgraduated professionals who are endeavored to demonstrate the role of vitamin D in many inflammatory disorders. Yet, at the same time, this should even suggest that there is not any particular intellectual property aside from that one coming from a general, shared interest in the issue as related to other specific areas, such as cancer, rheumatology, allergy, endocrinology, internal medicine. Therefore, the question is: why so much people is investigating the role of vitamin D in medicine?

A recent communication held by Professor William Grant from the Sunlight Nutrition and Health Research Center, San Francisco, CA, USA, concluded that solar UVB geographical exposure and 25(OH)vitD$_3$ (calcifediol or calcidiol) bioavailability, are causally linked in the presumptive reduction of cancer incidence and that an increase in plasma bioavailability up to 100 nmol/L 25(OH)vitD$_3$ should reduce notably cancer risk [1]. Vitamin D went in the spotlight because of its wondrous potential to prevent cancer onset, or even fight it. Interestingly, very few papers dealing with vitamin D in cancer have never reported in my University, despite the fact that some research teams (Table 1) would be pleased to test vitamin D on pancreas cancer, though they never published on pancreas oncology and have an ongoing expertise in adipose tissue and aging. An eclecticism, somewhat, in medical science, arouses researchers' curiosity on vitamin D, most probably because this vitamin exerts a particular appeal in clinical pathology. Sincerely, I think that vitamin D, particularly its main circulating form 25(OH)vitD$_3$, actually possesses many interesting properties but most probably they were overrated or, more simply, excessively simplified at the most common view.

The role of vitamin D in cancer prevention and treatment is yet a puzzling issue.

While an extensive, thorough scientific literature exists about the role of vitamin D in muscle and bone physiology, its latest emerging role as an anti-inflammatory agent suggested for a major role in chronic inflammatory pathologies, such as tumors [2]. The effect of calcidiol on tumors yet depends on a huge deal of factors, of which the availability and metabolism of calcitriol (1α,25(OH)$_2$vit D$_3$) is probably the main item [3]. Calcitriol is the active form of vitamin D, is the major ligand of the vitamin D receptor (VDR) and is rapidly degraded by 24-hydroxylases. To date, due to its very short plasma half-life, its analytical determination is particularly cumbersome and time expensive, so the activity of calcitriol is closely related to the bioavailability of its main precursor, 25(OH)vitD$_3$. However, the ability of calcidiol to exert its action as the dihydroxylated form, depends by VDR response in different cells, particularly in immune and cancer cells [3, 4]. Genetics of VDR in human population, such as Cdx2 (breast cancer), Fok1 (prostate cancer), BsmI, TaqI, ApaI, EcoRV VDR polymorphisms, has been reported to affect cancer onset and progression, when related to vitamin D availability and supplementation [5–7]. VDR polymorphism influences any vitamin D-mediated

Salvatore Chirumbolo[1]

Affiliations: [1]Department of Medicine-LURM, University of Verona, Policlinico GB Rossi, piazzale AL Scuro 10.

Corresponding Author: Dr. Salvatore Chirumbolo, Department of Medicine-LURM, University of Verona, Policlinico GB Rossi, piazzale AL Scuro 10, 37134 Verona, Italy; Ph: +390458128456; Fax: +390458027403; E-mail: salvatore.chirumbolo@univr.it

Received: 15 June 2015
Published: 01 August 2015

response in metabolic syndrome [8], islet autoimmunity and type 1 diabetes [9], gynecological malignancies [10], Th1 cell immunity [11], although association with VDR SNPs and type 1 diabetes at the genomic level showed also some contradictory evidence [12, 13]. If calcitriol acts as a hormonal and immunomodulating activity targeting VDR, its efficiency level in tumors should depend on VDR polymorphism, besides to any nutritional intake [3] and actually VDR polymorphism is a major issue to address cancer prevention and therapy [14].

Table 1: University of Verona: research team and co-authors studying the effect of vitamin D on human health

Department	Research group or coauthor	Main publications on vitamin d from the reasearch team	Topic and issues	Latest reports
Unit of Rheumatology, Department of Medicine, University of Verona, Italy	Prof. Silvano Adami	72	Rheumatology	Gatti D et al. Bone. 2015 May 14;78:212–215 Rossini M et al., Clin Exp Rheumatol. 2015 Jan-Feb;33(1):77–83
Department of Life and Reproduction Sciences, Pediatric Clinic, Faculty of Medicine, University of Verona, Verona, Italy	Prof. Attilio Boner Prof. Diego Peroni	20	Pediatric allergy	Franchi B et al Eur J Pediatr. 2015 Jun;174(6):749–57 Benettia C et al., Mini Rev Med Chem. 2015 May 19, in press Benetti C et al, Allergy Asthma Proc. 2015 Jan-Feb;36(1):19–25
Department of Medicine, Section of Endocrinology, Diabetes and Metabolism , Azienda Ospedaliera Universitaria Integrata, University of Verona , Verona , Italy	Prof. Enzo Bonora Prof Giovanni Targher	20	Endocrinology	Targher G, Byrne CD. Endocrine. 2014 Sep;47(1):3–4. Zoppini G et al. BMJ Open Diabetes Res Care. 2015 Apr 4;3(1):e000058
Department of Medicine, Clinic of Internal Medicine, Section D, University of Verona, Verona, Italy	Prof. Luca Dalle Carbonare	9	Bone research	Dalle Carbonare L et al., Transplantation. 2011 Jul 15;92(1):106–11
Department of Medicine, Section of Dermatology and Venereology, University of Verona, Verona, Italy	Prof. Gianpiero Girolomoni	6	Dermatology	Girolomoni G et al., G Ital Dermatol Venereol. 2012 Dec;147(6):609–24
Department of Medicine University of Verona, Verona, Italy	Dr. Andrea Dalbeni (co-author) Prof Pietro Minuz	4	Internal Medicine	Beveridge LA et al., JAMA Intern Med. 2015 May 1;175(5):745–54 Dalbeni A et al., Am J Cardiovasc Drugs. 2014 Oct;14(5):357–66
Department of Medicine, Section Geriatry, University of Verona , Verona , Italy	Prof. Mauro Zamboni Dr. Elena Zoico	3	Geriatry	Zoico E et al., Endocrinology. 2014 Nov;155(11):4178–88
CRR Fibrosi Cistica, Azienda Ospedaliero-universitaria di Verona, Verona, Italy	Dr. Barouk M Assael	3	Cystic fibrosis-Respiratory disease	Bianchi ML et al., Lancet Respir Med. 2013 Jul;1(5):377–85
Department of Life and Reproduction Sciences-Biochemical and Haematological Laboratoiry University of Verona, Verona Italy	Prof. Gian Cesare Guidi Prof. Gianluca Salvagno	2	Clinical biochemistry	Lippi G et al Acta Biomed. 2015 Apr 27;86(1):59–62
Division of Thoracic Surgery, Ospedale Maggiore Azienda Ospedaliera, Verona, Italy	Ddr A Norsa, D Martino	2	Cancer	Norsa A et al., Cancer Biother Radiopharm. 2007 Feb;22(1):50–5

Moreover, VDR is expressed also by immune cells and both calcidiol and calcitriol are able to modulate gene transcription in leukocytes, mainly T-helper and NK cells [15]. To date, no reports were published trying to address the complex relationship between VDR polymorphism and circulating levels of calcidiol, while this issue should be investigated in order to elucidate the apparently contradictory evidence coming from the employment of dietary-derived substances in cancer research [16, 17].

The fact that calcitriol is both a cytokine-like molecule and a hormone, should hamper any naïve approach taking into account vitamin D supplementation in cancer prevention or even treatment, even by arranging *in vitro* studies aiming at elucidating this relationship [18]. The relationship of circulating calcidiol and bioactive calcitriol appears to be the only mechanism to which any effort appears to be moved on, as a simplistic view considering that calcidiol is quite perfectly transformed in calcitriol, leads people to believe that a linear relationship between circulating calcidiol and active calcitriol can be reported. This might be quite far from the truth, although plasma level of calcidiol should give a "signal" of the individual endowment in active vitamin D_3. The question of how much plasma circulating calcidiol should warrant for a good prevention of chronic diseases, yet remains.

A more complex approach on vitamin D in cancer should involve issues such as (a) dietary habits in the studied/enrolled population, (b) lifestyles, (c) geographical area, (d) genetic polymorphism for VDR and P450 cytochromes, (e) gut microflora and gut microbiome (genomics).

Although this suggestion may be considered cumbersome for any good laboratory research on vitamin D, the simplest approach to test commercial colecalciferol or calcidiol on cancer cell lines cannot give important insights on the actual activity of calcidiol in people affected by tumors, particularly if research teams do not possess an excellent expertise in clinical oncology. Epidemiological investigations trying to highlight the relationship between plasma vitamin D levels and cancer onset and/or progression, are welcome but they must be read and understood at the light of differential dietary habits and geographical areas and furthermore an international consensus about the best plasma circulating calcidiol levels should be fitted to different geographical regions and/or different diet regimens and lifestyles, besides to age and sex.

Laboratories are hindered in their attempt to evaluate calcitriol dosage in biological fluids and therefore calcidiol, which accounts for a simplest way to evaluate its concentration, is quite the only reliable plasmatic parameter used to study vitamin D availability in humans. Any effort to relate clinical outcome to this marker does not take into consideration the fact that plasma calcidiol is in an homeostatic equilibrium with other forms and metabolites of vitamin D, particularly in chronic or immune degenerative disorders, although reports were published showing a certain linearity between calcidiol and calcitriol, which represents the current major prejudice [19, 20]. Furthermore, its relationship with innate and acquired immunity is yet highly complex [3, 4]. Whether vitamin D, in its active form, is either a protolerogenic or anti-inflammatory molecule, depends on its relationship with adipose tissue, muscle, bone and gut [3, 4], making a scenario that should render more complicated to ascertain the effect of vitamin D supplementation on cancer.

Therefore, maybe it is time at last to build up a multidisciplinar laboratory or research center in our University focused quite exclusively on vitamin D related disorders and translational medicine, based on vitamin D target, as the interest on the role exerted by vitamin D in the human health is greatly increasing in recent years.

Vitamin D probably does not heal people from cancer but, as many other natural-derived molecule, may greatly contribute to prevent its malignancy.

Keywords: Vitamin D, cancer, Verona University, pancreas

How to cite this article

Chirumbolo S. The research on vitamin D and cancer in Italy. Searching for an authorative expertise: The case of the University of Verona. Edorium J Pathol 2015;1:5–9.

Article ID: 100003P03SC2015

****

doi:10.5348/P03-2015-3-ED-2

****

Author Contributions

Salvatore Chirumbolo – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

REFERENCES

1. William B Grant. The role of solar UVB and vitamin D in reducing the risk of cancer and increasing survival. Homburg Effects of Light Congress, June 11-12, 2015, SUNARC San Francisco, CA, USA.
2. Pilz S, Gaksch M, Hartaigh BÓ, Tomaschitz A, März W. Vitamin D in preventive medicine. Anticancer Res 2015 Feb;35(2):1161–70.
3. Chirumbolo S. Vitamin D3 in cancer prevention and therapy: the nutritional issue. Horm Mol Biol Clin Investig 2015 Jun 9.
4. Chirumbolo S. Possible role of vitamin D3 on the adipocyte/fibroblast trans-differentiation mediated by pancreas cancer. Curr Health Sci J 2015; 41(1):5–10.
5. Pulito C, Terrenato I, Di Benedetto A, et al. Cdx2 polymorphism affects the activities of vitamin D receptor in human breast cancer cell lines and human breast carcinomas. PLoS One 2015 Apr 7;10(4):e0124894.
6. Atoum MF, AlKateeb D, AlHaj Mahmoud SA. The Fok1 vitamin D receptor gene polymorphism and 25(OH) D serum levels and prostate cancer among Jordanian men. Asian Pac J Cancer Prev 2015;16(6):2227–30.
7. Lee YH, Gyu Song G. Vitamin D receptor FokI, BsmI, TaqI, ApaI, and EcoRV polymorphisms and susceptibility to melanoma: a meta-analysis. J BUON 2015 Jan-Feb;20(1):235–43.
8. Schuch NJ, Garcia VC, Vívolo SR, Martini LA. Relationship between Vitamin D Receptor gene polymorphisms and the components of metabolic syndrome. Nutr J 2013 Jul 15;12:96.
9. Frederiksen B, Liu E, Romanos J, et al. Investigation of the vitamin D receptor gene (VDR) and its interaction with protein tyrosine phosphatase, non-receptor type 2 gene (PTPN2) on risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young (DAISY). J Steroid Biochem Mol Biol 2013 Jan;133:51–7.
10. Kahles H, Morahan G, Todd JA, Badenhoop K; Type I Diabetes Genetics Consortium. Association analyses of the vitamin D receptor gene in 1654 families with type I diabetes. Genes Immun. 2009 Dec;10 Suppl 1:S60–3.
11. Morán-Auth Y, Penna-Martinez M, Badenhoop K. VDR FokI polymorphism is associated with a reduced T-helper cell population under vitamin D stimulation in type 1 diabetes patients. J Steroid Biochem Mol Biol 2015 Apr;148:184–6.
12. Mun MJ, Kim TH, Hwang JY, Jang WC. Vitamin D receptor gene polymorphisms and the risk for female reproductive cancers: A meta-analysis. Maturitas 2015 Jun;81(2):256–65.
13. Morán-Auth Y, Penna-Martinez M, Badenhoop K. VDR FokI polymorphism is associated with a reduced T-helper cell population under vitamin D stimulation in type 1 diabetes patients. J Steroid Biochem Mol Biol 2015 Apr;148:184–6.
14. Gandini S, Gnagnarella P, Serrano D, Pasquali E, Raimondi S.Vitamin D receptor polymorphisms and cancer. Adv Exp Med Biol 2014;810:69–105.
15. Morán-Auth Y, Penna-Martinez M, Shoghi F, Ramos-Lopez E, Badenhoop K. Vitamin D status and gene transcription in immune cells. J Steroid Biochem Mol Biol 2013 Jul;136:83–5.
16. Paller CJ, Kanaan YM, Beyene DA, et al. Risk of prostate cancer in African-American men: Evidence of mixed effects of dietary quercetin by serum vitamin D status. Prostate 2015 Jun 5.
17. Tuohimaa P, Tenkanen L, Ahonen M, et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer 2004 Jan 1;108(1):104–8.
18. Zoico E, Franceschetti G, Chirumbolo S, et al. Phenotypic shift of adipocytes by cholecalciferol and 1a,25 dihydroxycholecalciferol in relation to inflammatory status and calcium content. Endocrinology 2014 Nov;155(11):4178–88.
19. Rejnmark L, Vestergaard P, Heickendorff L, Mosekilde L. Plasma 1,25(OH)2D levels decrease in postmenopausal women with hypovitaminosis D. Eur J Endocrinol 2008 Apr;158(4):571–6.
20. Shah I, Petroczi A, Naughton DP. Exploring the role of vitamin D in type 1 diabetes, rheumatoid arthritis, and Alzheimer disease: new insights from accurate analysis of 10 forms. J Clin Endocrinol Metab 2014 Mar;99(3):808–16.